Protocol

This trial protocol has been provided by the authors to give readers additional information about their work.

Protocol for: Ali K, Berman G, Zhou H, et al. Evaluation of mRNA-1273 SARS-CoV-2 vaccine in adolescents. N Engl J Med. DOI: 10.1056/NEJMoa2109522

This supplement contains the following items:

1. Summary of Protocol Changes; the Final Protocol (Amendment 1; March 23, 2021); the Original Protocol (Nov. 2, 2020)

2. The final Statistical Analysis Plan, version 2.0; Original Statistical Analysis Plan (Section 8 in the Final Protocol) - the summary of changes for the Statistical Analysis Plan is integrated into the Summary of Protocol Changes

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 6 28 Apr 2021	Amendment 6 28 Apr 2021
Amendment 5 19 Feb 2021	Amendment 5 19 Feb 2021
Amendment 4 15 Jan 2021	Amendment 4 15 Jan 2021
Amendment 3 02 Sep 2020	Amendment 3 02 Sep 2020
Amendment 2 01 Jul 2020	Amendment 2 01 Jul 2020
Amendment 1 18 May 2020	Amendment 1 18 May 2020
Original Protocol 22 Apr 2020	Original Protocol 22 Apr 2020

Amendment 6, 22 Apr 2021: Current Amendment

Main Rationale for the Amendment:

This protocol amendment will add an analysis at the end of Part A. An analysis of safety and immunogenicity data will be performed after all participants have completed Part A of the study. All data collected in Part A of the study will be cleaned (ie, data that are as clean as possible) and locked and a report may be generated as needed.

The summary of changes table provided here describes the major changes made in Amendment 6 relative to Amendment 5, including the sections modified and the corresponding rationales. The synopsis of Amendment 6 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes in Protocol Amendment 6:

Section # and Name	Description of Change	Brief Rationale
Synopsis and Section 4.7.6 (End of Study Analysis)	End of Part A clarified	To clarify that an analysis will be performed at the conclusion of Part A
Synopsis and Section 4.7.2 (analysis at End of Blined part A only)	Added an analysis of safety and immunogenicity at the end of Part A	To clarify that an analysis of safety and immunogenicity will be performed on all participants upon completion of Part A of the sutdy

Amendment 5, 19 Feb 2021

Main Rationale for the Amendment:

There is an urgent need for vaccination strategies against SARS-CoV2 that induce broader protection that includes variants such as B.1.351 to decrease morbidity and mortality. ModernaTX, Inc. is developing a mRNA vaccine (mRNA-1273.351) that is similar to the mRNA-1273 vaccine available under the Emergency Use Authorization (EUA), but in which the mRNA encodes for mutations included in the S protein of the B.1.351 variant.

This protocol amendment will add Part C to the protocol, which will be an amendment to investigate the proof of concept of a single dose booster of two dose levels of the mRNA-1273.351 variant and a mixture formulation of mRNA-1273/mRNA-1273.351 administered to approximately 60 participants who received primary vaccination during the mRNA-1273-P301 COVE study. The COVE study participants will be offered enrollment in this new site-specific sub study, Part C of mRNA-1273-P201, based on pre-determined eligibility criteria. If they choose to enroll in this protocol amendment, the participants will be discontinued from the mRNA-1273-P301 COVE study. The participants would have had to be originally randomized to the mRNA-1273 group and have previously received 2 doses of mRNA-1273, 28 days apart, to be enrolled in this amendment. The unblinding visit should also have occurred. In this protocol amendment, enrolled participants will be allocated 1:1:1 to receive a single intramuscular injection of mRNA-1273.351 (20 μg or 50 μg) or mRNA-1273/mRNA-1273.351 mixture (50 μg) as a booster injection.

The summary of changes table provided here describes the major changes made in Amendment 5 relative to Amendment 4, including the sections modified and the corresponding rationales. The synopsis of Amendment 5 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes in Protocol Amendment 5:

Section # and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval Page, Headers, Protocol Amendment Summary of Changes	Updated the protocol version and date.	To reflect the new version and date of the protocol.
Protocol Synopsis – Objectives and Section 2.7 (Primary Objectives [Part C, Open Label]), Section 2.8 (Secondary Immunogenicity Objective [Part C, Open Label]), and Section 2.9 (Exploratory Objectives [Part C, Open Label]	The description of the Part C primary, secondary, and exploratory objectives was added to the Protocol Synopsis. The description of Part C was included in Section 2 (Study Objectives). Section 2.7, Section 2.8, and Section 2.9 were added to encompass the addition of Part C primary, secondary, and exploratory objectives.	The addition of Part C was the main purpose of this amendment.
Protocol Synopsis – Study Design and Methodology and Section 3.1 (General Study Design)	A description of the general design of Part C was added to the synopsis. The description was also added to Section 3.1 for consistency.	The addition of Part C was the main purpose of this amendment. Language was included for consistency and clarity.
Protocol Synopsis – Study Design and Methodology and Section 3.1.3 (Part C, Open-Label Interventional Phase of mRNA-1273.351 and mRNA-1273/mRNA-1273.351 Mixture Booster Vaccines)	A further description of the methodology for Part C was included in the synopsis and Section 3.1.3 for consistency and clarity. Figure 4 was added to Section 3.1.3 as a visual aid for the structure of Part C.	The addition of Part C was the main purpose of this amendment. Language was included for consistency and clarity.
Protocol Synopsis – Safety Assessments and Section 3.4.7 (Safety Assessments)	Applicable safety assessments for Part C were indicated in the safety sections of the synopsis and body for consistency.	The addition of Part C was the main purpose of this amendment.
Protocol Synopsis – Immunogenicity assessments, Section 3.4.5 (Immunogenicity Assessments)	Part C immunogenicity assessments were included for clarity.	The addition of Part C was the main purpose of this amendment. Language added for clarity.
Protocol Synopsis – Investigational Product, Dosage, and Route of Administration and Section 3.3.3 (Identity of Investigational Product)	The investigational product, dosage, and route of administration information was provided for Part C.	The addition of Part C was the main purpose of this amendment. Language was included for clarity.
Protocol Synopsis – Investigational Product, Dosage, and Route of Administration and Section 3.3.5 (Blinding)	Specified that Part B and Part C of the study will be open label.	The addition of Part C was the main purpose of this amendment. Language was added for clarity and consistency.

Section # and Name	Description of Change	Brief Rationale
Protocol Synopsis – Sample Size and Section 4.5 (Sample Size Determination)	Clarified that patients in Part A will have the opportunity to enter Part B provided they meet the eligibility criteria. A description of the Part C sample size and enrollment process was provided.	Language was updated for clarity. The description for Part C was included as the addition of Part C was the main purpose of this amendment.
Protocol Synopsis – Statistical Methods and Section 4.6 Statistical Methods.	Indicated that Part C data may be presented separately, as appropriate. Specified when analyses were specific to Part A and Part B. Indicated that Part C will be similarly analyzed (when not specific to Part A and Part B).	Language was included as the addition of Part C was the main purpose of this amendment. Other language updated for clarity and consistency.
Protocol Synopsis – Study Analyses and Section 4.7.3 (Interim Study Analysis for Open-Label Part C Only)	Indicated that an interim analysis of the safety and immunogenicity data in Part C of the study may be performed after participants have completed OL-D8, OL-D15, OL-Day 29 and/or the OL-Day 57 study procedures. Section 4.7.3 added, and language included for consistency and clarity.	The addition of Part C was the main purpose of this amendment. Language was included for clarity.
Section 3.1.6 (Inclusion Criteria)	Section 3.1.6 heading was created. Inclusion criterion #7 was updated to #6 as there is no inclusion criterion #7. A separate set of inclusion criteria for Part C was included. Headers separating Parts A and B from Part C were created.	Headings were created for clarity and readability. Numbering was updated for clarity and accuracy. Part C inclusion criteria was added to clarify what participants will be eligible for Part C.
Section 3.1.7 (Exclusion Criteria)	A separate set of exclusion criteria for Part C was included. Headers separating Parts A and B from Part C were created.	Part C exclusion criteria was added to clarify which participants will not be eligible for Part C. Headers were created for clarity and readability.
Section 3.3.1 (Method of Assigning Participants to Dosing Groups [Part A and Part C])	Table 2 – Dose Group Assignment (Part C) added to clarify groups, investigational product, and number of participants.	The addition of Part C was the main purpose of this amendment. The table was added for clarity.

Section # and Name	Description of Change	Brief Rationale
Section 7.1 (Appendix 1: Schedule of Events) – Table 11 (Part B: Open-label Schedule of Events: ONLY for Participants Receiving 2 Doses of mRNA-1273 28 Days Apart)	"Blood for vaccine immunogenicity[4]" updated to "Blood for serology[9] and immunogenicity[4]" Added Footnote 9 "Blood sample for serology will be collected only at the Participant Decision Visit."	Language updated and footnote added for clarity and specificity of serology timing.

Section # and Name	Description of Change	Brief Rationale
Section 7.1 (Appendix 1: Schedule of Events) – Table 12 (Part B and Part C: Open-label Schedule of Events (Participants Receiving a Booster Dose)[9]	Table title updated to remove "ONLY for" and "single." "Blood for vaccine immunogenicity[5]" updated to "Blood for serology[10] and immunogenecity[5]" Updated note language to indicate the following, "Participants who decline receiving booster mRNA-1273, decline unblinding, or decline to receive 2 doses of mRNA-1273 in Part B will not receive study vaccination at OL-D1 (or OL-D29), will not perform a pregnancy test, or eDiary activation at OL-D1." Added Footnote 10 "Blood sample for serology will be collected only at the Participant Decision Visit (OL-D1)." Addition of Booster injection for Part C under OL-D57. Added footnote 11 "In Part C, an additional booster injection may be added approximately 56 days after the first boost at OL-D1. This additional booster dose will be triggered following review of immunogenicity data up to OL-D15 of the initial mRNA1273.351(20 and 50 µg) and mRNA-1273/mRNA-1273.351 mixture injections." Added footnote 12 "If the additional booster dose is given at OL-D57, an eDiary for reactogenicity will be completed for 7 days post-injection. Additionally, unsolicited AEs will continue to be collected for 28 days post last injection."	Title update made as this schedule of events applies to participants who choose to decline unblinding, but wish to remain in the study, decide to unblind but decline to receive further vaccination (either a single mRNA-1273 booster or 2 doses of mRNA-1273, 28 days apart). Language updates made for clarity and specificity of serology timing. An additional booster injection may be added approximately 56 days after the first boost at OL-D1. This will be determined following review of immunogenicity data up to OL-D15. Additional footnotes included for clarity.

Amendment 4, 15 Jan 2021

Main Rationale for the Amendment:

Following authorization of a COVID-19 vaccine under an Emergency Use Authorization (EUA), this study amendment is designed to transition to Part B, the Open-Label Interventional Phase (Figure 3). Transitioning the study to Part B, Open-Label Interventional Phase permits all ongoing study participants to (a) be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA, and (b) the option to offer all ongoing study participants who request unblinding an opportunity to schedule a study visit to know their original group assignment (placebo vs. mRNA-1273 [50µg or 100µg vaccine]).

Part B, Open-label Interventional Phase, also provides the opportunity for study participants who previously received placebo, to request to receive 2 doses of the mRNA-1273 (100 µg) vaccine. Participants who originally received 1 or 2 doses of mRNA-1273 (50µg or 100µg vaccine) during Part A, will have the opportunity to request to receive a single booster dose of mRNA-1273 (50 µg).

The summary of changes table provided here describes the major changes made in Amendment 4 relative to Amendment 3, including the sections modified and the corresponding rationales. The synopsis of Amendment 4 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes in Protocol Amendment 4:

Section # and Name	**Description of Change**	**Brief Rationale**
Title Page, Protocol Approval Page, Headers, Protocol Amendment Summary of Changes	Updated the protocol version and date	To reflect the new version and date of the protocol
Synopsis (Objectives) and Section 2 (Study Objectives)	Added objectives for Part B, Open Label	Added to specifically enumerate the objectives for the Open-Label part of the study, allowing for changes to study design and dosing.

Section # and Name	Description of Change	Brief Rationale
Synopsis (Study Design), Section 3.1.2 (Part B, Open-Label Interventional Phase), Section 7.1 (Appendix 1: Schedule of Events)	Added a "Participant Decision Clinic Visit"; instructions for transitioning to Part B, Open Label; Schedule of Events for the Participant Decision Clinic Visit; and Schedules of Events for Part B, Open-Label procedures.	This Participant Decision Clinic Visit provides the opportunity for study site personnel to discuss with and offer to participants, the choice to be unblinded, as well as offering to participants who originally received placebo, the choice to receive active vaccination with mRNA-1273 and possible vaccination against COVID-19, as well as offering those who received mRNA-1273 during Part A, the choice to receive a booster injection of mRNA-1273. The new Schedules of Events distinguish Part B, Open Label from Part A, Blinded, since all participants will transition to Part B. The Part B Schedules of Events provide procedural instructions for participants who will receive 2 mRNA-1273 injections and for those who will receive 1 mRNA-1273 injection in Part B.
Section 1.2 (Nonclinical Studies in Development of mRNA-1273) and Section 1.3 (Clinical Studies With Lipid Nanoparticle mRNA Vaccines)	Updated status of nonclinical studies, as well as ongoing clinical studies, including this study (mRNA-1273-P201) and the Phase 3 Study mRNA-1273-P301.	The status of the 3 clinical studies (one Phase 1, one Phase 2a, and the Phase 3 study) has changed since Amendment 3. In addition, the results of the interim analyses in the Phase 3 study of the primary efficacy endpoint (prevention of COVID-19 infection), a major secondary endpoint (prevention of severe COVID-19), and safety and reactogenicity endpoints are now available and are provided here. These results provide the justification for offering participants the opportunity to receive active investigational product (mRNA-1273) and the potential benefit of vaccination against COVID-19.

Section # and Name	Description of Change	Brief Rationale
Section 4.3.2 (Statistical Analyses, Part B, Open Label)	Addition of Part B, open-label statistical analyses	Lists the Part B, open-label endpoints. Major differences from the Part A endpoints/analyses were elimination of assessment of laboratory values, and distinguishing identical endpoints for 50 µg and 100 µg of mRNA-1273.
Section 3.4.5 (Blinding)	The study site staff, investigators, study monitors, and participants will remain blinded until the conclusion of the study. Changed to: The study site staff, investigators, study monitors, and participants will remain blinded until the initiation of Open-Label Part B.	Previous language is no longer applicable, since the study will be unblinded for Part B.
Section 3.4.2.1 (Pause Rules)	The pause-triggering rules that have been in effect for Part A, will not be applicable for Part B; however, participants will continue to be monitored for the pause rule criteria.	In December 2020, after review of both safety and efficacy data observed to date, the FDA granted Emergency Use Authorization (EUA) to Moderna's mRNA-1273 vaccine. Given this, the current pause rules as outlined cannot be applied effectively, as it is more likely that any serious safety signal would emerge from the ongoing large public vaccination campaigns. Moderna will still monitor for safety events in this study and will report to the Safety Monitoring Committee as appropriate.
Section 4.7.2 (Interim Analysis for Open-Label Part B Only)	Added an option IA following completion of OL-Day 29 and/or OL-Day 57 study procedures.	The IA would help inform of the benefit of participant receiving a booster dose.

Amendment 3, 02 Sep 2020

The main purpose of this amendment was to clarify that data can be analyzed in multiple batches based on availability of participants who have reached the Day 57 visit. The summary of changes table describes the major changes made in Amendment 3 relative to Amendment 2, including the sections modified and the corresponding rationales. Minor editorial or formatting changes are not included in this summary table.

Summary of Major Changes in Protocol Amendment 3:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, Synopsis, and header	Updated the protocol version and date	Reflect the new version and date of the protocol.
Synopsis, Section 3.1 Study Design	Deleted repeated text about Safety Monitoring Committee review before expansion in Cohort 2.	Editorial removal of redundant text.
Synopsis, Section 3.4.5 Blinding, Section 4.1 Blinding and Responsibility for Analyses, Section 4.7.1 Primary Study Analysis	Added information about potential participant populations to be included in the primary analysis of safety and immunogenicity after completion of Day 57 procedures.	Clarification that data can be analyzed in multiple batches based on availability of participants who have reached the Day 57 visit.
Synopsis, Section 4.6.2 Safety Analyses	Revisions to clarify that separate summaries of Grade 3 or higher solicited ARs are not planned.	Clarification of planned safety analyses.
Section 3.5.2 Use of Electronic Diaries, Section 7.1 Appendix 1: Schedule of Events (Table 7)	Added clarification about site follow-up of relevant safety events from eDiary entries (includes revisions to Footnote 12).	Clarification that follow-up by telephone of relevant safety events from eDiary entries is not the same as scheduled safety follow-up telephone calls.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	The acceptable window around the Day 29 visit has been clarified as + 7 days with no negative visit window.	Correction to reflect the minimum interval between vaccine administrations of 28 days.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	The footnotes and footnote numbering have been updated to accommodate the footnotes that were added with Amendment 2.	Editorial clarification.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 4 has been revised to clarify that study days for safety follow-up are relative to Day 1 vaccine administration.	Editorial clarification.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 5 has been revised to explain how to handle potential visit window overlap related to Visit 8.	Editorial clarification.
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Footnote 10 has been revised to clarify the timing of nasopharyngeal swab samples on vaccination days.	Editorial clarification.

Abbreviations: AE = adverse event; AR = adverse reaction; MAAE = medically attended adverse event; SAE = serious adverse event.

Amendment 2, 01 Jul 2020

Main Rationale for the Amendment:

The main purpose of this amendment was to change the statistical analysis plan by removing interim analyses and defining the Primary Study Analysis and EOS Analysis. The summary of changes table describes the major changes made in Amendment 2 relative to Amendment 1, including the sections modified and the corresponding rationales. Minor editorial or formatting changes are not included in this summary table.

Summary of Major Changes in Protocol Amendment 2:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, and header	Updated the protocol version and date	Reflect the new version and date of the protocol.
Synopsis, Section 3.1 Study Design, Section 3.5.2 Use of Electronic Diaries, Section 3.5.3 Safety Telephone Calls, Section 7.1 Appendix 1: Schedule of Events (including text, Table 7, and footnotes to Table 7)	Added eDiary questionnaires to the procedure for safety follow-up after the Day 57 visit, with completion of eDiary questionnaires alternating with safety telephone calls approximately every 2 weeks after the Day 57 visit.	Reduce the burden on study site personnel of completing safety follow-up by telephone.
Synopsis, Section 3.1 Study Design, Section 3.5.3 Safety Telephone Calls, Section 7.1 Appendix 1: Schedule of Events (footnote 12)	Added exposure to someone with known COVID-19 or SARS-CoV-2 infection and participant experience of COVID-19 symptoms to the list of events queried during scheduled safety telephone calls.	Improve surveillance for incidence of COVID-19 during the study.
Synopsis, Section 3.1 Study Design	End of Study definition was amended.	Minor clarification to define the End of Study.
Synopsis, Section 3.4.5 Blinding, Section 4.1 Blinding and Responsibility for Analyses, Section 4.7 Study Analyses, Section 4.7.1 Primary Study Analysis, Section 4.7.2 End of Study Analysis, Section 6.4 Clinical Study Reports	Added descriptions of the Primary Study Analysis and End of Study Analysis and respective clinical study reports, replacing descriptions of interim analyses and reports. The synopsis contains a new section.	Eliminate interim analyses in favor of a focus on the primary analysis.
Synopsis, Section 4.6 Statistical Methods	Stated that all analyses will be performed by treatment group overall (for the 2 cohorts combined) and for the 2 cohorts separately, unless specified otherwise.	Previous versions of the protocol had not included the overall analysis in statement of the standard scope of analysis.
Synopsis, Section 4.6.3 Immunogenicity Analyses	For the primary immunogenicity endpoint, geometric mean titer was changed to geometric mean.	Assays for bAb are under development. The reported values may or may not be titers; hence the protocol wording has been modified.

Section # and Name	Description of Change	Brief Rationale
Section 3.5.1 Assessment for SARS-CoV-2 Infection	Added instructions for asymptomatic patients who have a confirmed SARS-CoV-2 infection.	To clarify the steps for the investigator to follow when a participant is confirmed to have SARS-CoV-2 infection but is asymptomatic.
Section 3.5.8.8 Assessment of Severity	Decoupled life-threatening and Grade 4 in the severity assessment.	To adhere to CDISC guidance and align with case report form page.
Section 3.5.8.8 Assessment of Severity	Added clarification on when an AE is defined as serious.	To clarify when an AE is defined as serious.

Abbreviations: AE = adverse event; bAb = binding antibody; CDISC = Clinical Data Interchange Standards Consortium; eDiary = electronic diary; SARS-Cov-2 = Severe Acute Respiratory Syndrome coronavirus that causes COVID-19.

Amendment 1, 18 May 2020

Main Rationale for the Amendment:

The main purpose of this amendment was to incorporate the following modifications requested by the FDA Center for Biologics Evaluation and Research:

• Enhance monitoring of participants who are confirmed to have SARS-CoV-2 infection.
• Include a convalescent visit for participants with confirmed SARS-CoV-2 infection.
• Explore the mRNA-1273 vaccine efficacy in preventing asymptomatic SARS-CoV-2 infection.
• Update the Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to extend the follow-up to a full 12-month period after the second injection on Day 29 (Month 1).
• Decrease the highest dose of mRNA-1273 in the study from 250 μg to 100 μg.

The summary of changes table describes the major changes made in Amendment 1, including the sections modified and the corresponding rationale. Minor editorial or formatting changes are not included in this summary table.

Summary of Major Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title page, Signature page, and header	Updated protocol version and date.	Revised version and date of protocol.
Title page, Signature page, and header	Updated the protocol title.	Revised to reflect the current purpose of the study.
Synopsis and Section 2.3 Exploratory Objectives	Added an exploratory objective to evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection.	Request from the Health Authority.

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 2.3 Exploratory Objectives, Section 4.3.3 Exploratory Endpoints, Section 4.6.4 Exploratory Analyses	Revised wording for the exploratory objective/endpoint regarding spike protein-specific serum immunoglobulin class and subclass and neutralizing antibody in serum	Editorial change.
Synopsis, Section 3.1 Study Design, Study Flow Schema (Figure 1), Sentinel and Expansion Cohort Schema (Figure 2), Section 3.1.1 Rationale for Dose Selection, 3.4.1 Method of Assigning Participants to Dosing Groups. Dose Group Assignment (Table 1), 3.4.2 Investigational Product Administration, 4.5 Sample Size Determination	Decreased the highest dose of mRNA-1273 in the study from 250 µg to 100 µg.	Decreased based on the preliminary findings of the Phase 1 DMID study.
Synopsis and Section 3.1 Study Design	Deleted collection of nasopharyngeal swab samples at the Screening Visit (Day 0).	Editorial update for consistency with Schedule of Events (Table 7).
Synopsis and Section 3.1 Study Design	Deleted the number of visits at which participants will have blood samples collected.	Editorial update to avoid confusion as blood samples will be collected at different visits for safety and vaccine immunogenicity assessments.
Synopsis; Section 3.1 Study Design, Section 3.5.6 Blood Sampling Volumes (Table 3), Section 3.5.7 Safety Assessments, Section 3.5.8.6 Eliciting and Documenting Adverse Events, Section 4.3.1.2 Primary Immunogenicity Endpoint, Section 4.3.2 Secondary Endpoints, Section 4.7 Interim Analyses, Section 6.4 Clinical Study Reports, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated Month 7 and Month 13 visits to Day 209 and Day 394, respectively, to allow for 6-month and 12-month intervals, respectively, after the second injection on Day 29 (Month 1).	Request from the Health Authority.
Synopsis, Section 3.1 Study Design, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated the biweekly safety telephone calls from Day 211 through Day 351 to Day 223 through Day 377.	Consequent to the change made to the Day 209 Visit (Request from the Health Authority).

Section # and Name	Description of Change	Brief Rationale
Synopsis, Section 3.1 Study Design, Section 3.1.2 Rationale for Study Design, Section 3.5.1 Assessment for SARS-CoV-2 Infection, and Section 7.1 Appendix 1: Schedule of Events (Table 7)	Updated nasal swab to nasopharyngeal swab.	Clarified the type of swab to be performed.
Section 3.1.1 Rationale for Dose Selection	Updated enrollment and preliminary safety data from the ongoing Phase 1 DMID study.	Updated based on the preliminary findings of the Phase 1 DMID study.
Section 3.2.1 Inclusion Criteria	Updated inclusion criterion #7 to exclude sperm donations through 3 months after the last injection.	Update to align with the informed consent form on refraining male participants from sperm donation through 3 months after the last injection based on IRB feedback to the ICF.
Section 3.3.2 Handling Withdrawal From the Study	Updated the scheduled end of study assessments at Day 394 (Month 13) to allow for a 12-month interval after the second vaccination on Day 29 (Month 1).	Request from the Health Authority.
Section 3.4.5 Blinding	Updated the method to maintain the blind of the dosing assignment from opaque sleeve to blinding label.	Operational change in cases for which opaque sleeves are not used.
Section 3.5.1 Assessment for SARS-CoV-2 Infection	• Added more intense monitoring of participants who are confirmed to have SARS-CoV-2 infection (ie, notification of the participant's primary care physician by the investigator and recording of confirmed SARS-CoV-2 infection as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome). • Added a convalescent visit with blood collection after diagnosis of SARS-CoV-2 infection.	Request from the Health Authority.
Section 3.5.1 Assessment for SARS-CoV-2 Infection and Section 3.5.8.2 Medically Attended Adverse Event	Deleted "or COVID-19."	Editorial update for internal consistency.
Section 4.3.3 Exploratory Endpoints	Included a new exploratory endpoint to evaluate the effect of the mRNA-1273 vaccine on the incidence of SARS-CoV-2 infection.	Request from the Health Authority.

Section # and Name	Description of Change	Brief Rationale
Section 7.1 Appendix 1: Schedule of Events (Table 7)	Deleted that Day 0 and Day 1 visits may be combined the same day.	Editorial update of template text, which did not apply to this protocol.
	Corrected sequential footnote numbering in the schedule of events (Table 7).	Editorial update.
	Included a header row titled "Days Since Most Recent Vaccination."	Update to clarify that the visits are relative to the most recent injection.

Abbreviation: DMID = Division of Microbiology and Infectious Diseases; ICF = informed consent form; IRB = Institutional Review Board; MAAE = medically attended adverse event; SARS-Cov-2 = Severe Acute Respiratory Syndrome coronavirus that causes COVID-19.

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age
Protocol Number:	mRNA-1273-P203
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	Roderick McPhee, MD, PhD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: 1-617-301-1186 e-mail: Roderick.McPhee@modernatx.com
Regulatory Agency Identifier Number(s):	IND: 019745
Amendment Number:	1
Date of Amendment 1:	23 Mar 2021
Date of Original Protocol:	04 Nov 2020

CONFIDENTIAL

PROTOCOL APPROVAL – SPONSOR SIGNATORIES

Study Title:	A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age
Protocol Number:	mRNA-1273-P203
Amendment Number:	1
Amendment 1 Date:	23 Mar 2021

Protocol accepted and approved by:

See esignature and date signed on last page of document.

Roderick McPhee, MD
Clinical Development, Infectious Disease
ModernaTX, Inc
200 Technology Square
Cambridge, MA 02139
Telephone: 1-617-682-2724

Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age" and the most recent version of the investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current Protocol, the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without Institutional Review Board (IRB) approval except to eliminate an immediate risk to participants.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a sub-investigator. I will not supply study treatment to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the Sponsor or a partnership in which the Sponsor is involved. I will immediately disclose it in writing to the Sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the IRB. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from ModernaTX, Inc. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Signature of principal investigator	Date
Printed name of principal investigator	

Protocol Amendment Summary of Changes

DOCUMENT HISTORY	
Document	**Date**
Amendment 1	23 Mar 2021
Original Protocol	04 Nov 2020

Amendment 1, 23 Mar 2021: Current Amendment

Main Rationale for the Amendment:

The primary rationales for this amendment are as follows:

- To update the primary endpoints and null hypotheses (or success criteria) for establishing immunobridging and assumptions for the sample size calculations, as recommended by Health Authorities.
- Following the authorization of a COVID-19 vaccine under an Emergency Use Authorization (EUA), this study amendment is designed to transition to Part B, the Open-Label Observational Phase. Transitioning the study to Part B, the Open-label Observational Phase permits all ongoing study participants (a) to be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and (b) for EUA-eligible study participants, the opportunity to schedule a study visit to know their original group assignment (placebo versus mRNA-1273).
- Part B, the Open-label Observational Phase also provides the opportunity for study participants who previously received placebo to request to receive 2 doses of the mRNA-1273 vaccine.

The summary of changes table provided here describes the major changes made in Amendment 1 relative to the original protocol, including the sections modified and the corresponding rationales. The synopsis of Amendment 1 has been modified to correspond to changes in the body of the protocol.

Summary of Major Changes in Protocol Amendment 1:

Section # and Name	Description of Change	Brief Rationale
Title Page, Protocol Approval Page, Headers, Protocol Amendment Summary of Changes	Updated the protocol version and date.	To reflect the new version and date of the protocol.
Protocol Synopsis – Objectives and Section 2 (Objectives and Endpoints)	The primary endpoints were redefined. Secondary and exploratory endpoints were refined. An additional secondary objective and corresponding endpoint were added. A new exploratory objective and endpoint were added.	If an accepted threshold of protection is not available, using coprimary endpoints based on nAb geometric mean and seroresponse rate (added) in the noninferiority test was recommended by Health Authorities, as it is considered standard in immunobridging. A secondary objective/endpoint to evaluate asymptomatic SARS-CoV-2 infection was added to be separate from the objective/endpoint of SARS-CoV-2 infection in participants with SARS-CoV-2 negative at baseline. An exploratory objective/endpoint was added to evaluate asymptomatic SARS-CoV-2 infection in participants seropositive at baseline.
Protocol Synopsis – Overall Study Design, Section 3.1 (General Study Design), Section 3.1.1 (Part A, the Blinded Phase), Section 3.1.2 (Part B, the Open-label Observational Phase), and Section 7 (Study Assessments and Procedures)	The study design was updated to describe the updated crossover design of the study, including Part A (the Blinded Phase) and Part B (the Open-label Observational Phase).	The addition of the crossover design provides the opportunity for study participants to be informed regarding the EUA of mRNA-1273 for any persons under the age of 18 years, be unblinded to their original assignment (mRNA-1273 or placebo), and for those who previously received placebo to actively request to receive 2 doses of mRNA-1273 (100 µg) vaccine.
Protocol Synopsis – Study Duration and Section 3.1.1 (Part A, the Blinded Phase)	The study duration was clarified to reflect the differing study duration for participants who were initially randomly assigned to mRNA-1273 versus patients who were initially randomized to placebo but who opt to receive mRNA-1273 after unblinding.	The addition of the crossover design was one of the primary purposes of this amendment.
Protocol Synopsis – Inclusion Criteria and Section 4.1.1 (Inclusion Criteria)	Updated to allow abstinence as a contraception option and remove the criteria that participants not be currently breastfeeding	Updated to be consistent with the current standard of care in the United States.
Protocol Synopsis – Exclusion Criteria and Section 4.1.2 (Exclusion Criteria)	Updated to remove exclusion of participants with a known history of SARS-CoV-2 infection or contact with a confirmed case of SARS-CoV-2 infection.	Updated to be consistent with the current standard of care in the United States, and to address the increasing prevalence of SARS-CoV-2 infection and make

Section # and Name	Description of Change	Brief Rationale
		the study more consistent with the "real world" (EUA) setting.
Protocol Synopsis – Study Eligibility Criteria (Part B) and Section 4.2 (Study Eligibility Criteria, Part B)	Section added for Part B of the study to specify that participants participating in Part B must have been previously enrolled in the mRNA-1273-P203 study; and that female participants of childbearing potential may enroll in Part B if they have negative pregnancy tests at OL-Day 1 and OL-Day 29.	To establish separate eligibility criteria for Part B of the study.
Protocol Synopsis – Procedures and Assessments (Safety Assessments) and Section 7.1 (Safety Assessments and Procedures)	Updated to clarify the collection periods for ARs, AEs leading to discontinuation from dosing and/or study participation, MAAEs, SAEs, and AESIs.	To clarify based on the new crossover design of the study.
Protocol Synopsis – Procedures and Assessments (Immunogenicity Assessments) and Section 7.2 (Immunogenicity Assessments)	Updated to note the assessments for Parts A and B of the study, to clarify the analytes to be measured, and to add testing of serum for nAb and bAb against the SARS-CoV-2 S protein.	Revised the assessments and tests plan for the unbinding or participant decision visit and subsequent visits to be used for long-term follow-up analyses.
Protocol Synopsis – Procedures and Assessments (Efficacy Assessments) and Section 7.3.1 (Vaccine Effectiveness Assessments)	Updated to refine the Ab response assessment if an accepted threshold of protection is not available.	To define the coprimary endpoints required for the noninferiority test to establish immunobridging.
Protocol Synopsis – Statistical Methods (Hypothesis Testing) and Section 8.2 (Statistical Hypothesis)	Updated to redefine the study hypotheses based on updates to the coprimary endpoints.	To specify the hypotheses for the updated coprimary endpoints using noninferiority test.
Protocol Synopsis – Statistical Methods (Power and Sample Size) and Section 8.3 (Power and Sample Size)	Updated to reflect increases in the size of the Immunogenicity Subset for the purposes of establishing acceptable noninferiority margins.	To detail the sample size and power calculations for the updated primary endpoints and hypotheses.
Protocol Synopsis – Statistical Methods (Analysis Sets) and Section 8.4 (Analysis Sets)	Added mITT and miTT1 analysis sets.	To define mITT and mITT1 to be used in the sensitivity analyses of secondary efficacy endpoints.
Protocol Synopsis – Statistical Methods (Immunogenicity Analyses) and Section 8.5.3 (Immunogenicity Analyses)	Updated the analyses of the coprimary endpoints	To describe the analysis methods for the updated coprimary endpoints.
Protocol Synopsis – Statistical Methods (Efficacy Analyses) and Section 8.5.4 (Efficacy Analyses)	Updated to clarify the secondary efficacy analyses.	To clarify the secondary efficacy analyses.
Protocol Synopsis – Statistical Methods (Long-term Analysis) and Section 8.5.5 (Long-term Analysis)	Added section to describe long-term analyses of safety, efficacy, and immunogenicity data to include data collected during Part B of the study.	To describe long-term analyses including Part B data.
Protocol Synopsis – Study Analyses (Interim Analyses) and Section 8.6.1 (Interim Analyses)	Updated to indicate that more than one interim analysis may be performed, and to describe the	To support potential EUA in the adolescent age group.

Section # and Name	Description of Change	Brief Rationale
	timepoints at which the analyses will be performed.	
Section 1.2.2 (Clinical Studies)	Revised section to provide data for ongoing mRNA-1273 studies.	To harmonize section content with current status of development in the program.
Section 1.3.2 (Risks from Study Participation and Their Mitigation), 3.1.1 (Part A, the Blinded Phase), 5.3.2 (Administration of Study Vaccine), 7.1.1 (Use of Electronic Diaries), and 7.1.4 (Vital Sign Measurements)	Updated post-IP administration observation period from 60 minutes to 30 minutes.	Pursuant to cross-functional discussion and observation period of 15 minutes under the EUA.
Section 3.3 (Justification for Dose, Control Product, and Choice of Study Population)	Updated section to include justification for the crossover design.	The addition of the crossover design was one of the primary purposes of this amendment.
Section 5.3.2 (Administration of Study Vaccine)	Updated IP administration to include the IP administered in Parts A and B of the study.	The addition of the crossover design was one of the primary purposes of this amendment.
Section 6.2 (Discontinuing Study Vaccination)	Updated to remove the allowance for study removal for serology or RT-PCR testing positive for SARS-CoV2 for either Day 1 or for an illness visit.	Updated to be consistent with current standard of care in the US.
Section 6.4 (Study Pause Rules)	Updated to clarify that study pause rules are only applicable to Part A of the study but that participants will be monitored for the events leading to study pause during Part B of the study. Updated to clarify actions to be taken if thresholds for any pause rules are met. Updated to clarify that any Grade 3 or higher AEs meet event criteria.	To clarify safety assessments after crossover.
Section 7.1.1. (Use of Electronic Diaries)	Updated to clarify that eDiaries will only be used in Part A of the study.	The solicited AR profile will be sufficiently demonstrated in Part A; therefore, it is no longer necessary to collect additional data on solicited ARs following injection in the open-label phase.
Section 7.3.1 (Vaccine Effectiveness Assessments)	Updated to further define criteria for SARS-CoV-2 infection.	To clarify the definition of SARS-CoV-2 infection in participants who are SARS-CoV-2 negative at baseline.
Section 7.4.4.1 (Anaphylaxis)	Added section to characterize anaphylaxis and provide reporting requirements.	This text is being added to all mRNA-1273 protocols based on recent reports of anaphylaxis in the post-Emergency Use Authorization setting.
Section 7.4.5 (Adverse Events of Special Interest)	Updated to define an AESI and provide reporting requirements.	To provide more specific guidance to sites.

Section # and Name	Description of Change	Brief Rationale
Section 7.4.7 (Eliciting and Documenting Adverse Events)	Updated to clarify that solicited ARs will be collected only in Part A, and to define the end of study participation for the purposes of collection MAAEs and SAEs.	To provide more specific guidance to sites.
Section 8.1 (Blinding and Responsibility for Analyses)	Updated to describe unblinding procedures relevant to the interim analyses.	To clarify the blinding/unblinding plan and process.
Section 10.1 (Appendix 1: Schedule of Assessments)	Table 7 title updated to reflect Part A of the study. Updated study visit day D209 to "D209/Participant Decision Visit" Increased visit window for D209 to ±56 days. Increased visit window for the safety follow-ups (D223-D363) to ±3 days. Row added for revised informed consent/assent form. Added note to clarify the SoA to be followed after unblinding for participants who previously received mRNA-1273. Added footnote for time frame for Participant Decision Clinic Visit. Revised footnote to indicate that e-Diary recording will start approximately 30 minutes after injection.	To clarify as related to crossover design.
	Added table (Table 8) for the Participant Decision Clinic Visit.	To allow for participant unblinding and decision to receive mRNA-1273 if previously randomized to placebo.
	Added new SoA (Table 9) for Part B of the study.	To provide instructions for participants previously randomized to placebo who have elected to receive mRNA-1273 in Part B of the study.
	Added flow chart (Figure 4) between Parts A and B of the study.	To demonstrate participants' movement between Part A and Part B, and back to Part A.
Section 10.2.8 (Protocol Deviations)	Added guidance for participants' movement between Part A and Part B.	The addition of the crossover design was one of the primary purposes of this amendment.

Abbreviations: AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; CBER = Center for Biologics Evaluation and Research; D = day; eDiary = electronic diary; EUA = Emergency Use Authorization; IP = investigational product; MAAE = medically attended adverse event; mITT = modified intent-to-treat; nAb = neutralizing antibody; SAE = serious adverse event; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV2 = Severe Acute Respiratory Syndrome coronavirus 2; SoA = Schedule of Assessments.

IRB and Regulatory Authority Approval

A copy of this amended protocol will be sent to the institutional review board (IRB) and regulatory authority.

The changes described in this amended protocol require IRB approval prior to implementation. In addition, if the changes herein affect the informed consent, sites are required to update and submit a revised informed consent for approval that incorporates the changes described in this amended protocol.

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1273 for injection

Name of Active Ingredient: mRNA-1273

Protocol Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age

Protocol Number: mRNA-1273-P203

Study Period (years): Approximately 1 year

Phase of Development: Phase 2/3

Estimated date first participant enrolled: 30 Nov 2020

Estimated date last participant completed: 30 Jun 2022

Total Number of Sites: Approximately 15 to 25 study sites in the United States or its territories.

Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of 100 μg of mRNA-1273 vaccine administered in 2 doses 28 days apart	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs through the entire study period • AESI of MIS-C through the entire study period • Vital sign measurements

	• Physical examination findings
• To infer efficacy of mRNA-1273 (100 µg, 2 doses 28 days apart), serum Ab responses obtained 28 days after the second injection of mRNA-1273 (Day 57) will be either: – Evaluated against an accepted Ab threshold of protection against COVID-19 (if established in Study P301) – Compared in primary vaccine response as measured by GM values of serum Ab and seroresponse rate in P203 with those obtained from young adult recipients (18-25 years of age) of mRNA-1273 in the clinical endpoint efficacy trial (Study P301)	• The proportion of participants with a serum Ab level at Day 57 ≥ an Ab threshold of protection[1] • The primary vaccine response as measured by GM value of serum Ab level and seroresponse rate from Study P203 vaccine recipients at Day 57 compared with those obtained from young adult recipients (18-25 years of age) at Day 57 in the clinical endpoint efficacy trial (Study P301)[2] 1. If an accepted serum Ab threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy 2. If a threshold is not available, efficacy will be inferred based on establishing noninferiority of adolescent (12 to < 18 years; this clinical study) to adult GM values of serum Ab and seroresponse rate obtained in Study P301 (GM value 12 to < 18 years / GM value 18-25 years).
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of SARS-CoV-2 S2P-specific bAb through 1 year after Dose 2	• The GM value of SARS-CoV-2 S2P-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2)
• To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of nAb through 1 year after Dose 2	• The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2)
• To evaluate the effect of mRNA-1273 on the incidence of SARS-CoV-2	• The incidence of SARS-CoV-2 infection (symptomatic or asymptomatic infection)

infection compared with the incidence among placebo recipients	counted starting 14 days after the second dose of IP • SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline: – bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by Roche Elecsys) at Day 57 or later, OR – Positive RT-PCR counted starting 14 days after the second dose of IP
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) counted starting 14 days after the second dose of IP in participants with negative SARS-CoV-2 at baseline
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with SARS-CoV-2 infection AND positive RT-PCR for SARS-CoV-2	• The incidence of the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 is defined as symptomatic disease based on the following criteria: – The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥ 100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR – The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND – The participant must have at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if

	hospitalized) positive for SARS-CoV-2 by RT-PCR
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence and comparison of bAb and nAb titers against isolated strain relative to prototype vaccine strain
• To describe the ratio or profile of specific bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x, and 4x rise of bAb relative to baseline

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; GM = geometric mean; GMFR = geometric mean fold-rise; IP = investigational product; LLOQ = lower limit of quantification; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; nAb = neutralizing antibody; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; S2P = S protein; SAE = severe adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

Overall Study Design

This is a two-part, Phase 2/3, study: Part A and Part B. The study will evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) vaccine in healthy adolescents 12 to < 18 years of age.

Participants in Part A, the Blinded Phase of the study, will be randomly assigned to receive injections of either 100 µg of mRNA-1273 vaccine or a placebo control in a 2:1 randomization ratio. Part B, the Open-label Observational Phase of this study, is designed to offer participants who received placebo in Part A of this study, and who meet EUA eligibility criteria, an option to receive mRNA-1273 in an open-label fashion.

The goal of the study is to seek an indication for use of mRNA-1273 (100 µg intramuscular [IM], given as 2 injections, 28 days apart) in the 12 to < 18 years age group. The basis for demonstrating vaccine effectiveness is proposed to be met by serum antibody (Ab) response

measured in this adolescent age group. The approach to inferring vaccine effectiveness will depend on whether an accepted serum Ab threshold conferring protection against coronavirus disease 2019 (COVID-19) has been established. If an Ab threshold of protection has been established, effectiveness will be inferred based on the proportion of adolescent study participants with serum Ab levels (on Day 57) that meet or exceed the Ab threshold. If an Ab threshold of protection has not been established, effectiveness will be inferred by demonstrating noninferiority of both the (i) geometric mean (GM) value of serum neutralizing antibody (nAb) and (ii) the seroresponse rate from adolescent participants compared with those from young adults (18-25 years of age) enrolled in the ongoing clinical endpoint efficacy trial (Study P301).

Part A, the Blinded Phase

This study in adolescents will monitor all participants for a total of 12 months following the second dose of vaccine or placebo. Safety assessments will include solicited adverse reactions (ARs; 7 days after each injection), unsolicited adverse events (AEs; 28 days after each injection), medically attended adverse events (MAAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) (multisystem inflammatory syndrome in children [MIS-C]) throughout the study period.

Blood samples will be collected from all participants at baseline (Day 1), Day 57 (28 days after Dose 2), Day 209 (6 months after Dose 2), and Day 394 for measurement of SARS-CoV-2 specific binding and nAb responses. Blood samples will also be tested for the development of Ab directed against nonvaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2.

The incidence of SARS-CoV-2 infection among vaccine recipients and placebo recipients will be compared to assess the potential for mRNA-1273 to reduce the rate of infection in vaccine recipients.

Part A comprises 8 scheduled visits including a screening visit and 7 scheduled visits, of which Visit 2 and Visit 4 will be virtual/telephone visits and the other visits will be in-clinic visits. This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

Part B, the Open-label Observational Phase

Part B, the Open-label Observational Phase of the study, will be prompted by the authorization of a COVID-19 vaccine under an Emergency Use Authorization (EUA) for any persons under the age of 18 years. Participants will be transitioned to Part B of the study as their age group becomes EUA-eligible. This transition permits all ongoing study participants to eventually be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and the option to offer all ongoing study participants an opportunity to schedule

a Participant Decision Visit to know their original treatment assignment (placebo vs. mRNA-1273 100 µg vaccine).

Part B provides the opportunity for study participants to be informed regarding the EUA, be unblinded to their original assignment (mRNA-1273 or placebo), and for those who previously received placebo to actively request to receive 2 doses of mRNA-1273 (100 µg) vaccine. EUA-eligible study participants will receive a Notification Letter summarizing the basis for EUA of a COVID-19 vaccine to receive an EUA and will be asked to schedule a Participant Decision Clinic Visit.

At the Participant Decision Clinic Visit, EUA-eligible participants will:

- Be given the option to be unblinded as to their original group assignment (placebo vs. mRNA-1273 vaccine [100 µg]),
- Be counseled about the importance of continuing other public health measures to limit the spread of disease including social distancing, wearing a mask, and hand-washing,
- Sign a revised informed consent form and assent, and
- Provide a nasopharyngeal (NP) swab for RT-PCR for SARS-CoV-2 and a blood sample for serology and immunogenicity.

After the Participant Decision Clinic Visit, participants will follow the Part A SoA or Part B SoA as follows:

- Participants received placebo in Part A and consent to unblinding and to receiving 2 doses of mRNA-1273 in Part B: These participants will proceed to Part B and follow the Part B SoA.
- Participants received 2 doses of mRNA-1273 in Part A and consent to unblinding: Due to statistical considerations, these participants will be considered as entering Part B (the Open-label Observational Phase) but will continue to follow the Part SoA.
- Participants decline unblinding: These participants will remain in Part A and follow the Part A SoA.

Safety Oversight:

Safety oversight will be under the direction of a Data Safety Monitoring Board composed of external independent consultants with relevant expertise.

The contract research organization's medical monitor, the Sponsor's medical monitor, and the individual study site investigators will monitor safety throughout the study.

Study Duration:

The study duration will be approximately 14 months, which includes 1 month for screening (Day -28 to Day 1), 1 month for dosing (on Day 1 and Day 29), and, for participants who received mRNA-1273 in Part A, 12 months of follow up after the second dose to monitor for safety, immunogenicity, and efficacy. Participants who received placebo in Part A will still be in the study for approximately 14 months total but will be followed for approximately 5 months following their second dose of mRNA-1273 in Part B.

Number of Participants: Approximately 3,000 participants will be enrolled.

Study Eligibility Criteria (Part A):

Inclusion Criteria:

Each participant must meet all of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, 12 to < 18 years of age at the time of consent (Screening Visit, Day 0) who, in the opinion of the investigator, is in good general health based on review of medical history and screening physical examination.
2. Investigator assessment that the participant, in the case of an emancipated minor, or parent(s)/legally acceptable representative(s) understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures and provides written informed consent/assent.
3. Body mass index (BMI) at or above the third percentile according to World Health Organization (WHO) Child Growth Standards at the Screening Visit (Day 0).
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche or surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy).
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test at Screening (Day 0), on the day of the first injection (Day 1), and on the day of the second injection (Day 29)
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1)
    - Has agreed to continue adequate contraception or abstinence through 3 months following the second injection (Day 29)

Exclusion Criteria:

Participants who meet any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Travel outside of the United States in the 28 days prior to the Screening Visit (Day 0).
2. Pregnant or breastfeeding.
3. Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion

may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.

4. Prior administration of an investigational CoV (eg, SARS-CoV-2, Severe Acute Respiratory Syndrome coronavirus [SARS-CoV], Middle East Respiratory Syndrome coronavirus [MERS-CoV]) vaccine.
5. Current treatment with investigational agents for prophylaxis against COVID-19.
6. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
7. Current use of any inhaled substance (eg, tobacco or cannabis smoke, nicotine vapors).
8. History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).
9. History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of screening.
10. History of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
    - Congenital or acquired immunodeficiency, including human immunodeficiency virus (HIV) infection
    - Suspected active hepatitis
    - Has a bleeding disorder that is considered a contraindication to IM injection or phlebotomy
    - Dermatologic conditions that could affect local solicited AR assessments
    - History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine
    - Diagnosis of malignancy within the previous 10 years (excluding nonmelanoma skin cancer)
    - Febrile seizures
11. Receipt of:
    - Any licensed vaccine within 28 days before the first dose of IP or plans for receipt of any licensed vaccine through 28 days following the last dose of IP.
    - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 20 mg/day prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days

prior to the day of enrollment. Participants may have visits rescheduled for enrollment if they no longer meet this criterion within the Screening Visit window. Inhaled, nasal, and topical steroids are allowed.

- Intravenous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrollment.

12. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.
13. Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.
14. Is an immediate family member or has a household contact who is an employee of the research center or otherwise involved with the conduct of the study.

Study Eligibility Criteria (Part B):

1. Participants must have been previously enrolled in the mRNA-1273 P203 study.

2. Female participants of childbearing potential may be enrolled in the study if the participant has a negative pregnancy test on the day of the first injection (OL-Day 1) and on the day of the second injection (OL-Day 29).

Study Treatment:

Investigational Product:

The investigational product (mRNA-1273 vaccine) is a lipid nanoparticle (LNP) dispersion of a messenger RNA (mRNA) encoding the prefusion stabilized spike (S) protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). mRNA-1273 injection is provided as a sterile liquid for injection, white to off-white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

Mode of Administration:

Doses will be administered by IM injection into the deltoid muscle according to the procedures specified in the mRNA-1273-P203 Pharmacy Manual. Preferably, both doses should be administered into the nondominant arm.

Procedures and Assessments:

Safety Assessments:

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days) in Part A. Solicited ARs will be recorded daily using electronic diaries (eDiaries).
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days)
- AEs leading to discontinuation from dosing and/or withdrawal from study participation from Day 1 through the last day of study participation (ie, Day 394 per Part A SoA and OL-Month 7 in Part B)
- MAAEs from first dose on Day 1 through the entire study period (ie, Day 394 per Part A SoA and OL-Month 7 in Part B)
- SAEs from first dose on Day 1 through the entire study period (ie, Day 394 per Part A SoA and OL-Month 7 in Part B)
- AESI of MIS-C through the entire study period (ie, Day 394 per Part A SoA and OL-Month 7 in Part B)
- Vital sign measurements
- Physical examination findings
- Assessments for SARS-CoV-2 infection from Day 1 through study completion
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study

Immunogenicity Assessments:

The following analytes will be measured in blood samples for immunogenicity assessments:

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays
- Serum binding antibody (bAb) levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein
- Serum bAb levels against SARS-CoV-2 nucleocapsid protein as measured by ligand-binding assay specific to the SARSCoV2 nucleocapsid protein

Serum collected from all participants will be tested for bAb against SARS-CoV-2 nucleocapsid protein at specified time points. In addition, serum samples from a selected subset of study participants who received mRNA-1273 will be selected for testing of nAb and bAb against the SARS-CoV-2 S protein.

Efficacy Assessments:

Vaccine effectiveness for adolescents of ages of 12 to < 18 years will be inferred based on serum Ab responses obtained on Day 57 (28 days after the second injection of mRNA-1273). Inference will be based on assessing the adolescent Ab responses against the following:

1. *If available at the time of analysis*, adolescent Ab responses will be assessed against an accepted serum Ab threshold conferring protection against COVID-19.
2. *If an accepted threshold of protection is not available*, adolescent Ab responses will be assessed by establishing noninferiority of the GM value and seroresponse rate of serum nAb from adolescent participants compared with those from young adults enrolled in the ongoing clinical endpoint efficacy trial (Study P301).

Statistical Methods:

Hypothesis Testing:

If an accepted serum Ab threshold of protection against COVID-19 is established for the primary immunogenicity objective, the null hypothesis is that the percentage of participants on mRNA-1273 with serum Ab equal to or above the established threshold at Day 57 is ≤ 70% (ie, H_0: percentage of participants on mRNA-1273 ≤ 70% with serum Ab at Day 57 equal to or above the established threshold).

The study would be considered as meeting the immunogenicity objective if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 70% (lower bound of the 95% CI > 70%).

If an accepted serum Ab threshold of protection against COVID-19 is not available for the primary immunogenicity objective, the immunogenicity analysis of primary vaccine response will be performed using the noninferiority tests of the two null hypotheses based on the two coprimary endpoints, respectively.

Coprimary endpoint 1: Ab GM at Day 57

H^1_0: immunogenicity response to mRNA-1273 as measured by Ab GM at Day 57 is inferior in adolescents (12 to < 18 years of age) compared with that in young adults (18-25 years of age) using mRNA-1273 Study P301 data.

The noninferiority in Ab GM in adolescents compared with that in young adults (18-25 years of age) is demonstrated by that the lower bound of the 95% CI of the GMR rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5. The GMR is the ratio of the GM value of adolescents on mRNA-1273 in this study, Study P203, at Day 57 compared with the GM value of young adults (18-25 years of age) on mRNA-1273 in Study P301.

Coprimary endpoint 2: Ab seroresponse rate at Day 57

A definition of seroresponse will be provided in the statistical analysis plan (SAP) based on forthcoming information about assay performance.

The null hypothesis:

H^2_0: immunogenicity response to mRNA-1273 as measured by seroresponse rate at Day 57 is inferior in adolescents (12 to < 18 years of age) compared with that in young adults (18-25 years of age) using mRNA-1273 Study P301 data.

The noninferiority in seroresponse rate in adolescents compared with that in young adults (18-25 years of age) is demonstrated by that the lower bound of the 95% CI of the seroresponse rate difference rules out -10% (ie, lower bound > -10%) using the noninferiority margin of 10%. The seroresponse rate difference is defined as the rate in adolescents receiving mRNA-1273 minus the rate in young adults (18-25 years of age) receiving mRNA-1273 from Study P301.

The study would be considered as meeting the primary immunogenicity objective if noninferiority is demonstrated based on both coprimary endpoints.

Details regarding the assay to be used to assess noninferiority will be provided in the SAP.

Power and Sample Size:

The sample size of this study is driven by safety. Approximately 3,000 participants will be randomly assigned in a 2:1 ratio to receive mRNA-1273 or placebo. With 2,000 participants exposed to mRNA-1273, the study has at least 90% probability to observe at least 1 participant with an AE at a true 0.25% AE rate.

Serum samples from all participants will be collected and banked, a subset of participants will be selected, and their samples will be processed for immunogenicity testing (the Immunogenicity Subset).

Approximately 362 participants who receive mRNA-1273 will be selected for the Immunogenicity Subset, with a target of 289 participants receiving mRNA-1273 in the Per-Protocol (PP) Immunogenicity Subset (adjusting for approximately 20% of participants who may be excluded from the PP Immunogenicity Subset, as they may not have immunogenicity results due to any reason). The sample size of the Immunogenicity Subset may be updated with

data from other mRNA-1273 studies or external data especially regarding a threshold of protection. In such a situation, the final sample size of the Immunogenicity Subset will be documented in the SAP.

For the primary immunogenicity objective, with approximately 289 participants in the PP Immunogenicity Subset, the study will have > 90% power to rule out 70% with a 2-sided 95% CI for the percentage of mRNA-1273 participants exceeding the acceptable threshold if the true rate of participants exceeding the acceptable threshold is 80%.

If an acceptable Ab threshold of protection against COVID-19 is not available at the time of analysis, for the primary immunogenicity objective, noninferiority tests of two null hypotheses based on two coprimary endpoints, respectively, will be performed. The sample size calculation for each of the two noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants in the PP Immunogenicity Subset in Study P203 and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) from Study P301, there will be 90% power to demonstrate noninferiority of the immune response as measured by Ab GM in adolescents in Study P203 at a 2-sided alpha of 0.05, compared with that in young adults (18-25 years of age) from Study P301 receiving mRNA-1273, assuming an underlying geometric mean ratio (GMR) value of 1 and a noninferiority margin of 1.5. The standard deviation (SD) of the log-transformed levels is assumed to be 1.5.
- With approximately 289 participants in the PP Immunogenicity Subset in Study P203 and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) from Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by seroresponse rate in adolescents in Study P203 at a 2-sided alpha of 0.05, compared with that in young adults of (18-25 years of age) from Study P301 receiving mRNA-1273, assuming true seroresponse rate of 85% in young adults (18-25 years of age) from Study P301, and a true seroresponse rate of 85% in adolescents in Study P203 (ie, true rate difference is 0 compared to young adults [18-25 years of age] from Study P301), and a noninferiority margin of 10%.

Analysis Sets:

The analysis sets are defined in the following table:

Analysis Set	Description
Randomization Set	All participants who are randomized, regardless of the participants' treatment status in the study.

Full Analysis Set (FAS)	All randomized participants who received at least 1 injection of IP.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing.
Per-protocol (PP) Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset who received planned doses of study vaccination per schedule, complied with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. Participants who are seropositive at baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for analyses of immunogenicity unless specified otherwise.
PP Set for Efficacy	All participants in the FAS who received planned doses of study vaccination, had no immunologic or virologic evidence of prior COVID-19, and have no major protocol deviations that impact key or critical efficacy data.
Solicited Safety Set	The Solicited Safety Set consists of FAS participants who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Safety Set	All randomized participants who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for the solicited ARs.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline
Modified Intent-to-Treat-1 (mITT1) Set	All participants in the mITT Set excluding those who received the wrong treatment (ie, at least 1 dose received in Part A is not as randomized).

Abbreviations: AR = adverse reaction; bAb = binding antibody; COVID 19 = coronavirus disease 2019; FAS = full analysis set; IP = investigational product; mITT = modified intent-to-treat; PP = per protocol; RT-PCR = reverse transcription polymerase chain reaction.

Safety Analyses:

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by treatment group.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to withdrawal, vital sign measurements, and physical examination findings. The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be summarized.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each dose will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from IP or withdrawal from the study will be summarized. Unsolicited AEs will be presented by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class.

The number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summary tables accordingly.

Immunogenicity Analyses:

The SAP will describe the complete set of immunogenicity analyses, including the approach to sample participants into an Immunogenicity Subset for analysis of immunogenicity. The PP Immunogenicity Subset is the primary analysis set for immunogenicity unless otherwise specified. The primary immunogenicity objective of this study is to use the immunogenicity response to infer efficacy in adolescents (12 to < 18 years in this study).

If an accepted serum Ab threshold of protection against COVID-19 is available based on data from other mRNA-1273 studies or external data, the number and percentage of participants with Ab greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. If the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity objective of this study will be considered to be met.

The percentage of participants with serum Ab greater than or equal to the threshold with 95% CI will be provided at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum Ab threshold of protection against COVID-19 is not established, the non-inferiority of primary vaccine response as measured by Ab GM and seroresponse rate in

adolescents compared with those in young adults (18-25 years of age) receiving mRNA-1273 will be assessed. The study is considered as meeting the primary immunogenicity objective if the noninferiority of the immune response to mRNA-1273 as measured by both GM and seroresponse rate at Day 57 is demonstrated in adolescents in this study at a 2-sided alpha of 0.05, compared with that in young adults (18-25 years of age) in Study P301 receiving mRNA-1273.

An analysis of covariance model will be carried out with Ab value at Day 57 as a dependent variable and a group variable (adolescents in Study P203 and young adults [18-25 years of age] in Study P301) as the fixed variable. The GM values of the adolescents at Day 57 will be estimated by the geometric least squares mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. A corresponding 2-sided 95% CI will be provided to assess the difference in immune response for the adolescents in Study P203 compared to the young adults (18-25 years of age) in Study P301 at Day 57. The noninferiority of immune response to mRNA-1273 as measured by GM will be considered demonstrated if the lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5.

The number and percentage (rate) of participants achieving Ab seroresponse at Day 57 will be summarized. The difference of seroresponse rates between adolescents receiving mRNA-1273 in Study P203 and young adults (18-25 years of age) receiving mRNA-1273 in Study P301 will be calculated with 95% CI. The noninferiority in seroresponse rate of adolescents in Study P203 compared to young adults (18-25 years of age) in Study P301 will be considered demonstrated if the lower bound of the 95% of the seroresponse rate difference is > -10%, based on the noninferiority margin of 10%.

In addition, the GM level of specific nAb and bAb with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log transformed values then back transformed to the original scale. The geometric mean fold-rise of nAb and bAb with corresponding 95% CI will be provided at each time point with Day 57 as the primary time point of interest. Descriptive summary statistics including median, minimum, and maximum will also be provided.

Efficacy Analyses:

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate will be provided by vaccination group, calculated as the number of cases divided by the total person-time. The incidence rate ratio of mRNA-1273 versus placebo will be provided with 95% CI computed using the exact method conditional upon the total number of cases adjusted by the total person-time.

For SARS-CoV-2 infection (serologically confirmed SARS-CoV-2 infection or COVID-19), regardless of symptomatology or severity, infection rate will be provided by vaccination group. The infection rate ratio of mRNA-1273 versus placebo may be provided with its 95% CI using the exact method conditional upon the total number of cases adjusted by the total person-time. The incidence rate of asymptomatic SARS-CoV-2 infection will also be provided.

The secondary efficacy analyses will be performed in the PP set, with sensitivity analyses in the FAS, mITT Set, and mITT1 Set.

Long-Term Analysis:

Long-term analysis will be performed including data collected in the Open-label Observational Phase (Part B). Long-term analysis of applicable safety, efficacy, and immunogenicity endpoints will be summarized descriptively by treatment cohort without treatment group comparison.

In the long-term safety analysis, unsolicited AEs will be summarized.

In the long-term immunogenicity analysis, nAb and bAb values will be summarized at specified timepoints.

In the long-term efficacy analysis, the incidence rates of COVID-19 and of SARS-CoV-2 infection cases will be counted starting 14 days after the second dose of IP for participants in treatment cohorts of mRNA-1273 and Placebo, or starting 14 days after the second dose of mRNA-1273 for participants in the Placebo-mRNA-1273 cohort. Incidence rate with 95% CI adjusting for person-time will be provided. The incidence rate of asymptomatic SARS-CoV-2 infection will also be provided.

Study Analyses:

Interim Analyses:

More than one interim analysis may be performed. The first interim analysis of safety in this study will be performed when approximately 250 participants 16-17 years of age have completed Day 57 (1 month after Dose 2, Part A).

The interim analysis of immunogenicity and safety data will be performed after participants in an Immunogenicity Subset and a subset of all participants have completed Day 57 study procedures (in Part A), including all required immunogenicity data for the primary immunogenicity analysis. This interim analysis will be considered the primary analysis of immunogenicity. At the Sponsor's discretion, a clinical study report (CSR) may be developed for the interim analysis.

Final Analysis:

The final analysis of all applicable endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in a final CSR, including individual listings.

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LIST OF ABBREVIATIONS AND TERMS

The following abbreviations and terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
AR	adverse reaction
bAb	binding antibody
BMI	body mass index
CBER	Center for Biologics and Evaluation Research
CD	cluster of differentiation
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRO	contract research organization
CRP	C-reactive protein
CSR	clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
ERD	enhanced respiratory disease
ESR	erythrocyte sedimentation rate

Abbreviation or Specialist Term	Definition
EUA	Emergency Use Authorization
FAS	full analysis set
FDA	US Food and Drug Administration
FIO2	fraction of inspired oxygen
GCP	Good Clinical Practice
GLSM	geometric least squares mean
GM	geometric mean
GMFR	geometric mean fold-rise
GMR	geometric mean ratio
GMT	geometric mean titer
HCP	healthcare practitioner
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IL-6	interleukin 6
IM	intramuscular(ly)
IP	investigational product
IRB	institutional review board
LAR	legally acceptable representative
LDH	lactic acid dehydrogenase
LNP	lipid nanoparticle
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MIS-C	multisystem inflammatory syndrome in children

Abbreviation or Specialist Term	Definition
MN	microneutralization
mRNA	messenger RNA
nAb	neutralizing antibody
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NP	nasopharyngeal
Study P301	Study mRNA-1273-P301; NCT04470427
PaO2	partial pressure of oxygen
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000
PP	per protocol
QA	quality assurance
RT-PCR	reverse transcriptase polymerase chain reaction
S	spike
S2P	S protein
SAE	serious adverse event
SAP	statistical analysis plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SD	standard deviation
SM-102	eptadecane-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
SMC	Safety Monitoring Committee
SoA	schedule of assessments
SpO2	oxygen saturation
Study P301	Study mRNA-1273-P301; NCT04470427
Th1	T helper cell 1
Th2	T helper cell 2

Abbreviation or Specialist Term	Definition
WHO	World Health Organization
WOCBP	woman of childbearing potential

1. INTRODUCTION

1.1. Study Rationale

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Coronaviruses are zoonotic, meaning they are transmitted between animals and people. An outbreak of the CoV disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 215 other countries, territories, and areas including the United States (WHO 2020a). On 11 Mar 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic. As of 28 Sep 2020, the WHO dashboard (WHO 2020b) reported there have been nearly 1 million COVID-19 deaths worldwide and more than 200,000 deaths in the United States.

As of 21 Sep 2020, the US Centers for Disease Control and Prevention (CDC) reported over 6.7 million confirmed and probable cases of COVID-19 in all 50 states and 5 jurisdictions, with over 199,000 attributed and probable deaths (CDC 2020a). While the CDC have reported that the highest risk of disease burden is in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease, the burden in the pediatric population is not negligible. Rather, evidence is emerging (described below) to suggest that children < 18 years of age, particularly adolescents, may be disproportionately contributing to the number of new cases as schools re-open for varying degrees of in-person learning. As of 21 Sep 2020, the CDC reported over 408,000 cases of COVID-19 in children less than 18 years of age (8.1% of all US cases) and 88 deaths (< 0.1% of all US deaths; CDC 2020b).

During the incubation period, those infected can also transmit the virus (Chen et al 2020). Person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual, whether symptomatic or not (Rothan and Byrareddy 2020; Chen et al 2020; Licciardi et al 2020; Shen et al 2020). SARS-CoV-2 can also be transmitted via the fecal-oral pathway (Cruz and Zeichner 2020).

During this COVID-19 pandemic, children throughout much of the world have had school attendance limited in an attempt to control infection. Therefore, the main source of infection for SARS-CoV-2 in children, with or without clinical symptoms, is infected household contacts. Indeed, a retrospective cohort study of high school students, parents and siblings of students, and school staff conducted in France in early April 2020 suggests that there was little to no transmission from infected students to other students or school staff. Rather, a high prevalence of antibodies (Abs) against SARS-CoV-2 among families suggests familial clustering of COVID-19 cases (Fontanet et al 2020).

A recent report of COVID-19 trends in school-aged children in the United States from 01 Mar 2020 to 19 Sep 2020 indicates that 37% of laboratory-confirmed cases of COVID-19 in school-aged children occurred in children 5 to 11 years of age while 63% occurred in adolescents 12 to 17 years of age (Leeb et al 2020). During this time period, the average weekly incidence among adolescents was 37.4 cases per 100,000 compared with 19.0 per 100,000 for younger children. Among school-aged children with laboratory-confirmed COVID-19, 58% reported at least one symptom and 5% reported no symptoms; although information on symptoms was missing or unknown for 37%. Overall, in this study, 1.2% of school-aged children with COVID-19 were hospitalized, 0.1% required intensive care unit (ICU) admission and < 0.01% died of COVID-19. Furthermore, at least one underlying condition was reported in 3% of adolescents and 2% of younger children. Chronic lung disease, including asthma, was most commonly reported (55%), followed by disability (neurologic or neurodevelopmental disorders, intellectual or physical disability, and vision or hearing impairment; 9%), immunosuppressive conditions (7%), diabetes (6%), psychological conditions (6%), cardiovascular disease (5%), and severe obesity (4%) (Leeb et al 2020).

Another study examined the age distribution of COVID-19 in the United States from May to August 2020 based on 3 indicators: COVID-19-like illness-related emergency department visits, positive reverse transcriptase polymerase chain reaction (RT-PCR) results for SARS-CoV-2, and confirmed COVID-19 cases (Boehmer et al 2020). These authors report an estimated mean COVID-19 incidence during this time period of 179.3 cases per 100,000 in individuals 10 to 19 years of age. Generally, the largest increase in incidence during this time period was observed in persons < 30 years of age. Finally, a recent report describes an adolescent (13-year-old female), whose only symptom was nasal congestion, yet who was the index case in an outbreak of COVID-19 across 4 states (Schwartz et al 2020). Infection of this primary individual led to 11 subsequent cases, during July and August 2020, in 5 households all linked to a family gathering suggesting that adolescents can serve as the source of COVID-19 outbreaks within families, even when their symptoms are mild as in this case.

Taken together, the above evidence suggests that the burden of COVID-19 has begun to increase in younger age groups, particularly as schools in the United States have started to reopen for some in-person instruction. Adolescents, who are often mobile and may demonstrate lower compliance with nonpharmaceutical interventions such as mask-wearing and social distancing, also likely represent a segment of the population contributing toward sustained community transmission of SARS-CoV-2 and may spread SARS-CoV-2 within households. A vaccine that prevents COVID-19 and SARS-CoV-2 transmission in adolescents would be a crucial public health tool to help curb the pandemic.

There is currently no vaccine licensed to prevent SARS-CoV-2, and there is an urgent public health need to develop one, there being no proven therapy. ModernaTX, Inc (the Sponsor) has initiated an accelerated development program for mRNA-1273 vaccine against SARS-CoV-2 infection (Section 1.2), most recently initiating a Phase 3 clinical study in the United States involving administration of mRNA-1273 vaccine 100 µg as both an initial dose and a second dose 28 days later (Section 1.2.2).

The objective for this Phase 2/3 study is to evaluate the safety and reactogenicity of a single dose level (100 µg) of mRNA-1273 vaccine administered in 2 doses 28 days apart (Section 3.1) to an adolescent population. Recently, a fractional second dose administered intramuscularly (IM) has been assessed with an adjuvanted malaria vaccine and demonstrated similar immunogenicity with improved efficacy in a controlled human malaria infection model (Regules et al 2016; Moon et al 2020).

1.2. Background and Overview

The Sponsor has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then display protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. Messenger RNA vaccines have been used to induce immune responses against infectious pathogens such as SARS-CoV-2 (NCT04283461, NCT04405076), cytomegalovirus (NCT03382405), metapneumovirus and parainfluenza virus type 3 (NCT03392389), Zika virus (NCT03325075), and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). mRNA-1273 encodes for the full-length spike (S) protein of SARS-CoV-2. The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies (nAb) that prevent infection (Johnson et al 2016; Wang et al 2015; Wang et al 2018; Chen et al 2017; Corti et al 2015; Yu et al 2015; Kim et al 2019; Widjaja et al 2019; Corbett et al 2020a; Ju et al 2020; Robbiani et al 2020). It has been confirmed that the stabilized SARS-CoV-2 S protein (S2P) expresses well and is in the prefusion conformation (Wrapp et al 2020).

The development of the mRNA-1273 vaccine is being accelerated to address the current SARS-CoV-2 outbreak as a result of the uniquely rapid and scalable manufacturing process for mRNA-1273 vaccine.

1.2.1. Nonclinical Studies

Nonclinical studies have demonstrated that CoV S proteins are immunogenic and S protein-based vaccines, including those based on mRNA delivery platforms, are protective in animals. Prior clinical studies of vaccines targeting related CoVs and other viruses have demonstrated that mRNA-based vaccines are safe and immunogenic. mRNA-1273 has shown preliminary evidence of protection against SARS-CoV-2 in studies in young mice (Corbett et al 2020a) and nonhuman primates (NHPs) (Corbett et al 2020b).

In support of the development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing SM-102 (eptadecane-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

A detailed review of nonclinical experience with mRNA-1273 vaccine is provided in the investigator's brochure (IB).

1.2.2. Clinical Studies

The safety and immunogenicity of mRNA-1273 were evaluated in Phase 1 (DMID 20-0003) and Phase 2 (mRNA-1273-P201) studies that were important to select and to confirm the dose of the vaccine used in the pivotal Phase 3 study. In Study 20-0003 (Phase 1), 2 doses of 100 µg or higher generated the highest titers of nAb or binding antibody (bAb) with an acceptable safety profile, and this observation was the basis for selecting the 100-µg dose for use in the pivotal Phase 3 study. Importantly, the Ab levels after 2 doses of mRNA-1273 exceeded those from a pool of convalescent sera. Neutralizing activity was observed for the 100-µg mRNA-1273 dose as of Day 36 and was higher than that of the convalescent sera control group, and the median titers remained in the same range as the median titer in the convalescent sera control group at Day 119 across the age strata. In this study, the majority of the solicited ARs were mild or moderate. A higher incidence of severe solicited ARs was observed with the 250-µg dose (in the 18-55 year age cohort) compared with the lower doses (25 µg, 50 µg, and 100 µg); thus, the mRNA-1273 250-µg dose was not evaluated in participants ≥56 years of age. One severe unsolicited adverse event (AE) related to mRNA-1273 and 1 severe clinically meaningful elevation in serum lipase related to mRNA-1273 were also observed with the 250-µg dose (in the 18-55 year age cohort). Additionally, in Study 20-0003, T helper cell 1 (Th1)-directed CD4+ T-cells were observed to be induced across age groups, with limited indication of a T helper cell 2 (Th2)-directed response, and similar responses were observed among all age groups for the 100-µg dose. The predominance of a Th1-directed T cell profile helps mitigate concern of the risk of enhanced disease associated with Th2-driven pathophysiology.

In the dose-confirming Study mRNA-1273-P201 (Phase 2a), generally comparable nAb and bAb responses were measured in the serum of participants who received either 50-µg or 100-µg doses of mRNA-1273 administered 28 days apart, and an acceptable safety profile was observed. At all visits for mRNA-1273 groups, the geometric mean fold-rise (GMFR) in the anti-spike glycoprotein concentrations was greater in the 18 to 55-year age cohort than in the ≥ 55-year-old age cohort. For microneutralization (MN) titers, the geometric mean titer (GMT) and GMFR at Day 29 were higher in the 18 to 55-year-old age cohort than in the ≥ 55-year-old age cohort. The MN titer values at Day 43 and Day 57 were similar between age cohorts. Participants who received 2 doses of either 50 or 100 µg of mRNA-1273 separated by 28 days developed both bAb and nAbs against the SARS-CoV-2 virus, with GMFRs > 20-fold for bAb levels and > 50-fold for MN assay titers, regardless of dose level. These data are supportive because of the magnitude of the Ab response to 2 doses of mRNA-1273 and confirm the selection of the 100-µg dose brought forward in the pivotal Phase 3 efficacy study.

Currently, a Phase 3 pivotal, randomized, placebo-controlled, observer-blind clinical study (mRNA-1273-P301; NCT04470427; Study P301) is being conducted in participants 18 years of age and older who are at an increased risk of COVID-19 disease. In addition, prespecified cohorts of participants who were either ≥ 65 years of age or 18 to < 65 years of age with comorbid medical conditions were included. A total of 30,351 participants were followed for a median of 92 days (range: 1-122) for the development of COVID-19 disease. Success criteria for early efficacy were met at first interim analysis based on 95 adjudicated cases with a vaccine efficacy of 94.5% (95% CI: 86.5%, 97.8%; one-sided p-value < 0.0001). Study P301 is expected to provide immunogenicity data where an Ab threshold of protection against COVID-19 will be estimated.

In Study P301, solicited adverse reactions (ARs) were reported more frequently among vaccine participants than placebo participants. The most frequently reported ARs after any dose in the vaccine group were pain at the injection site (92.0% any grade; 6.1% grade ≥ 3), fatigue (70% any grade; 10.1% grade ≥ 3), headache (64.7% any grade; 5.7% grade ≥ 3), myalgia (61.5% any grade; 9.1% grade ≥ 3) and chills (45.4% any grade; 1.4% grade ≥ 3). The majority of local and systemic ARs had a median duration of 1 to 3 days. Overall, there was a higher reported rate of some ARs in younger age groups: the incidence of axillary swelling/tenderness, fatigue, headache, myalgia, arthralgia, chills, nausea/vomiting, and fever was higher in adults aged 18 to < 65 years than in those aged 65 years and above. Grade 3 solicited local ARs were more frequently reported after Dose 2 than after Dose 1. In the participants who received the vaccine, solicited systemic ARs were reported numerically more frequently by vaccine participants after Dose 2 than after Dose 1. Grade 3 systemic ARs (fatigue, myalgia, arthralgia, and headache) were reported more frequently after Dose 2 than after Dose 1. Unsolicited AEs and serious adverse events (SAEs) were reported at generally similar rates in participants who received mRNA-1273 and placebo from the first dose until the last observation. Unsolicited AEs that occurred in ≥ 1% of study participants who received

mRNA-1273 and at a rate at least 1.5-fold higher rate than placebo, were lymphadenopathy-related events (1.1% of versus 0.6%). All of the lymphadenopathy events are similar to the axillary swelling/tenderness in the injected arm reported as solicited ARs. Hypersensitivity AEs were reported in 1.5% of vaccine recipients and 1.1% of placebo recipients. Hypersensitivity events in the vaccine group included injection site rash and injection site urticaria, which are likely related to vaccination. There have been no cases of severe hypersensitivity or anaphylactic reactions reported immediately after vaccination in the trial to date. There were 3 reports of Bell's palsy in the mRNA-1273 vaccine group (one of which was an SAE), which occurred 22, 28, and 32 days after vaccination, and one in the placebo group, which occurred 17 days after vaccination. The currently available information on Bell's palsy is insufficient to determine a causal relationship with the vaccine. There were 2 SAEs of facial swelling in vaccine recipients with a history of injection of dermatological fillers. The onset of swelling was reported 1 and 2 days, respectively, after vaccination and was likely related to vaccination. There was 1 SAE of intractable nausea and vomiting in a participant with prior history of severe headache and nausea requiring hospitalization. This event occurred 1 day after vaccination and was likely related to vaccination.

There were no other notable patterns or numerical imbalances between treatment groups for specific categories of AEs (including other neurologic, neuro-inflammatory, and thrombotic events) that would suggest a causal relationship to mRNA-1273.

The Sponsor submitted a data package to FDA on 30 November 2020 for consideration of Emergency Use Authorization (EUA). FDA granted an EUA for mRNA-1273 for use in adults 18 years of age and older on 18 December 2020.

In the post-EUA period, anaphylaxis has been reported following mRNA-1273 administration.

A detailed review of the clinical experience with LNPs containing SM-102 (mRNA vaccines and placebo) is provided in the IB.

1.3. Benefit/Risk Assessment

1.3.1. Potential Benefits from Participation

The following benefits may accrue to participants:

- The mRNA-1273 vaccine may be an effective vaccine against COVID-19.
- Participants will have a baseline (Day 1) evaluation for SARS-CoV-2 infection and ongoing surveillance for COVID-19 throughout the study.
- The study will contribute to the development of a vaccine against COVID-19 for adolescents.

1.3.2. Risks from Study Participation and Their Mitigation

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 30 minutes after injection.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection and is not related to the substance injected. Therefore, it is important that standard precautions and procedures are followed to avoid injury from fainting.

Intramuscular injection with other mRNA vaccines manufactured by the Sponsor containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of injection.

The majority of local and systemic solicited ARs observed after injection with mRNA-1273 at the 100 µg dose level have been mild to moderate in severity (Section 1.2.2). The most commonly reported systemic ARs were headache, myalgia, fatigue, chills, and fever. In the majority of cases, the reactions resolved spontaneously within several days.

There is a theoretical risk that active vaccination to prevent SARS-CoV-2 infection may cause a paradoxical increase in the risk of COVID-19. This possibility is based on the rare phenomenon of vaccine-associated disease enhancement, which was first seen in the 1960s with 2 vaccines made in the same way (formalin-inactivated whole virus) and designed to protect children against infection with respiratory syncytial virus (Chin et al 1969) or measles virus (Fulginiti et al 1967). Disease enhancement has also been proposed as a possible explanation for cases of more serious disease associated with dengue vaccination (Thomas and Yoon 2019; WHO 2019).

In order to address this theoretical risk, animal studies were performed in young and aged wild-type mice and rhesus macaques (NHPs). These studies were designed to capture immunogenicity endpoints that would be predictive of enhanced respiratory disease (ERD) and also to evaluate if, at protective or subprotective dose levels of mRNA-1273, evidence of disease enhancement would be observed after challenge of the animals with SARS-CoV-2. These nonclinical studies demonstrated that mRNA-1273 is safe and well-tolerated in different animal species, is immunogenic; drives a robust SARS-CoV-2-specific Ab, neutralization, and Th1-directed cluster of differentiation (CD)4 T-cell response; fully protects animals from challenge at dose levels as low as 1 µg/dose in mice and 30 µg/dose in NHPs; and does not lead to ERD at protective or subprotective dose levels (Corbett et al 2020a; Corbett et al 2020b). Clinical immunogenicity data from the DMID Phase 1 study of mRNA-1273 demonstrated high levels of nAbs and Th1-polarized CD4+ T-cell responses (Jackson et al 2020), consistent with the immunogenicity

observed in these nonclinical studies. These data suggest that a paradoxical increase in the risk of disease, while not eliminated, is likely to be low.

1.3.3. Overall Benefit/Risk Conclusion

All participants will receive a single dosage of 100 μg of mRNA-1273 vaccine or placebo administered in 2 doses 28 days apart (Section 3.1).

Safety will be monitored throughout the study (Section 7.5).

Considering the lack of approved vaccines for COVID-19, the participants' risk of COVID-19 outside the study during a pandemic, and the nonclinical and clinical data to date, the Sponsor considers the potential benefits of participation to exceed the risks.

2. OBJECTIVES AND ENDPOINTS

The objectives which will be evaluated in this study and endpoints associated with each objective are provided in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs through the entire study period • AESI of MIS-C through the entire study period • Vital sign measurements • Physical examination findings
• To infer efficacy of mRNA-1273 (100 µg, 2 doses 28 days apart), serum Ab responses obtained 28 days after the second injection of mRNA-1273 (Day 57) will be either: – Evaluated against an accepted Ab threshold of protection against COVID-19 (if established in Study P301) – Compared in primary vaccine response as measured by GM values of serum Ab and seroresponse rate in P203 with those obtained from young adult recipients (18-25 years of age) of mRNA-1273 in the clinical endpoint efficacy trial (Study P301)	• The proportion of participants with a serum Ab level at Day 57 ≥ an Ab threshold of protection[1] • The primary vaccine response as measured by GM value of serum Ab level and seroresponse rate from Study P203 vaccine recipients at Day 57 compared with those obtained from young adult recipients (18-25 years of age) at Day 57 in the clinical endpoint efficacy trial (Study P301)[2] 1. If an accepted serum Ab threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy 2. If a threshold is not available, efficacy will be inferred based on establishing noninferiority of adolescent (12 to < 18 years; this clinical study) to adult GM values of serum Ab and seroresponse rate obtained in Study P301 (GM value 12 to < 18 years / GM value 18-25 years)

Objectives	Endpoints
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 μg) administered in 2 doses 28 days apart, as assessed by the level of SARS-CoV-2 S2P-specific bAb through 1 year after Dose 2	• The GM value of SARS-CoV-2 S2P-specific bAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2)
• To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 μg) administered in 2 doses 28 days apart, as assessed by the level of nAb through 1 year after Dose 2	• The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after Dose 2), Day 209 (6 months after Dose 2), and Day 394 (1 year after Dose 2)
• To evaluate the effect of mRNA-1273 on the incidence of SARS-CoV-2 infection compared with the incidence among placebo recipients	• The incidence of SARS-CoV-2 infection (symptomatic or asymptomatic infection) counted starting 14 days after the second dose of IP • SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline: – bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive (as measured by Roche Elecsys) at Day 57 or later, OR – Positive RT-PCR counted starting 14 days after the second dose of IP
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo	• The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) counted starting 14 days after the second dose of IP in participants with negative SARS-CoV-2 at baseline

Objectives	Endpoints
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with SARS-CoV-2 infection AND positive RT-PCR for SARS-CoV-2	• The incidence of the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 is defined as symptomatic disease based on the following criteria: – The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥ 100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR – The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND – The participant must have at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence and comparison of bAb and nAb titers against isolated strain relative to prototype vaccine strain
• To describe the ratio or profile of specific bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)
• To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline	• GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x, and 4x rise of bAb relative to baseline

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; GM = geometric mean; IP = investigational product; LLOQ = lower limit of quantification; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; nAb = neutralizing antibody; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; S2P = S protein; SAE = severe adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

3. STUDY DESIGN

3.1. General Design

This is a two-part, Phase 2/3 study: Part A and Part B. Participants in Part A, the Blinded Phase of the study, are blinded to their treatment assignment.

Part B, the Open-label Observational Phase of this study, is designed to offer participants who received placebo in Part A of this study and who meet the EUA eligibility criteria an option to receive mRNA-1273 in an open-label fashion (Figure 2). Participants who received mRNA-1273 (100 µg) in Part A of this study will proceed to Part B after they are unblinded and will continue to follow the Part A Schedule of Assessments (SoA). This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

3.1.1. Part A, the Blinded Phase

The blinded phase of this study is a randomized, observer-blind, placebo-controlled study intended to infer the effectiveness of mRNA-1273 in an adolescent population aged 12 to < 18 years. The study includes 2 arms: (i) 100 µg of mRNA-1273, and (ii) placebo. Approximately, 3,000 participants between 12 to < 18 years of age will be randomly assigned in a 2:1 ratio to receive mRNA-1273 (n=2,000) or placebo (n=1,000).

The schematic of study arms and major study events for Part A is illustrated in Figure 1 and the SOA for Part A is located in Table 7.

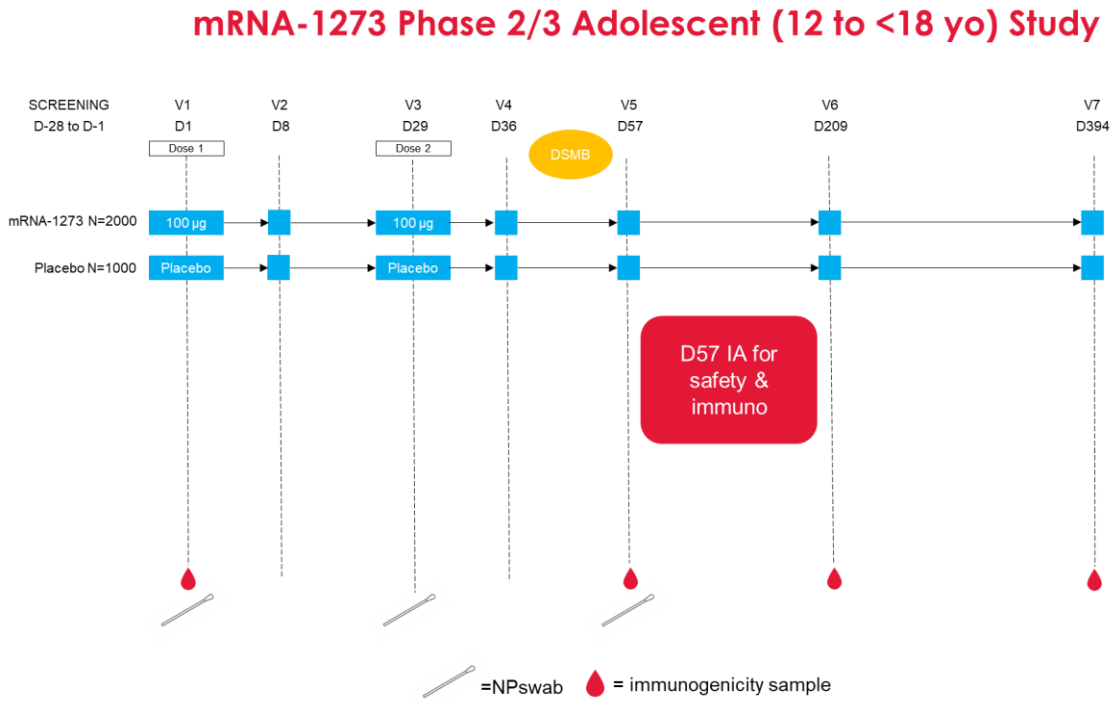
The goal of the study is to seek an indication for use of mRNA-1273 (100 µg IM, given as 2 injections, 28 days apart) in the 12 to < 18 years age group. The basis for demonstrating vaccine effectiveness is proposed to be met by serum Ab response measured in this adolescent age group. The approach to inferring vaccine effectiveness will depend on whether an accepted serum Ab threshold conferring protection against COVID-19 has been established. If an Ab threshold of protection has been established, effectiveness will be inferred based on the proportion of adolescent study participants with serum Ab levels (on Day 57) that meet or exceed the Ab threshold. If an Ab threshold of protection has not been established, effectiveness will be inferred by demonstrating noninferiority of both (i) the geometric mean (GM) value of serum nAb and (ii) the seroresponse rate from adolescent participants compared with those from young adults (18-25 years of age) enrolled in the ongoing clinical endpoint efficacy trial (Study P301). The statistical parameters to infer effectiveness are described in Section 2.

This study in adolescents will monitor all participants for a total of 12 months following the second dose of vaccine or placebo. Safety assessments will include solicited ARs (7 days after each injection), unsolicited AEs (28 days after each injection), medically attended adverse events

(MAAEs), SAEs, and adverse events of special interest (AESIs) (multisystem inflammatory syndrome in children [MIS-C]) throughout the study period.

Blood samples will be collected from all participants at baseline (Day 1), Day 57 (28 days after Dose 2), Day 209 (6 months after Dose 2), and Day 394 for measurement of SARS-CoV-2-specific bAb and nAb responses. Blood samples will also be tested for the development of Ab directed against non-vaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2. The incidence of SARS-CoV-2 infection among vaccine recipients and placebo recipients will be compared to assess the potential for mRNA-1273 to reduce the rate of infection in vaccine recipients.

Figure 1: Study Schema (Part A, Blinded Phase)



Abbreviation: D = day; DSMB = Data Safety Monitoring Board, IA = interim analysis, immuno = immunogenicity, NP = nasopharyngeal, V = visit, yo = years old.

Part A, the Blinded Phase of the study, comprises 8 scheduled visits including a screening visit and 7 scheduled visits, of which Visit 2 and Visit 4 will be virtual/telephone visits and the other visits will be in-clinic visits.

The study duration will be approximately 14 months, which includes 1 month for screening (Day -28 to Day 1), 1 month for dosing (on Day 1 and Day 29), and, for participants who received mRNA-1273 in Part A, 12 months of follow up after the second dose to monitor for safety,

immunogenicity, and efficacy. Participants who received placebo in Part A will still be in the study for approximately 14 months total but will be followed for approximately 5 months following their second dose of mRNA-1273 in Part B.

Note: Day 0 and Day 1 may be combined on the same day (Table 7).

After providing informed consent/assent, participants will undergo screening assessments to determine study eligibility. Screening assessments (Table 7) must be completed after signing the informed consent form (ICF)/assent form. The investigator will review study entry criteria to determine the participant eligibility during the Screening Period.

Eligible participants will enter the Treatment Period.

On Day 1, after the completion of the scheduled assessments (Table 7), participants will be administered a single IM dose of mRNA-1273 (100 µg) or placebo (procedures will be detailed in the mRNA-1273-P203 Pharmacy Manual). Participants will be closely monitored for safety and will remain at the study site for observation for at least 30 minutes after dosing. On Day 29, the second dose of investigational product (IP) will be administered. Participants will be monitored for 12 months after the second dose of IP for safety and immunogenicity assessments.

To test for the presence of SARS-CoV-2 by RT-PCR, nasopharyngeal (NP) swab samples will be collected on each day of injection prior to dosing and on Day 57 (28 days postdose 2), according to the SoA (Table 7).

During the course of the study, participants who meet prespecified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment, including an NP swab sample to be tested for the presence of SARS-CoV-2 by RT-PCR. Confirmed, symptomatic cases of SARS-CoV-2 infection will be captured as MAAEs and reported in an expedited time frame to the Sponsor (Section 7.3.3).

All participants will be monitored for safety and reactogenicity and provide pre- and postdose blood specimens for immunogenicity through 12 months after the second dose of mRNA-1273.

Participants will be instructed on the day of the first dose (Day 1) and reminded on the day of the second dose (Day 29) how to document and report solicited local or systemic ARs in a provided electronic diary (eDiary). Solicited ARs, unsolicited AEs, MAAEs, AEs leading to withdrawal, AESIs, and SAEs will be assessed as described in Section 7.1, according to the time points in the SoA (Table 7).

Blood sampling for immunogenicity testing is scheduled throughout the study: on the day of injection before the first dose and 1, 6, and 12 months after the second dose.

Participants may experience AEs that necessitate an unscheduled visit, including situations when the investigator asks a participant to return to the study clinic for an unscheduled visit following

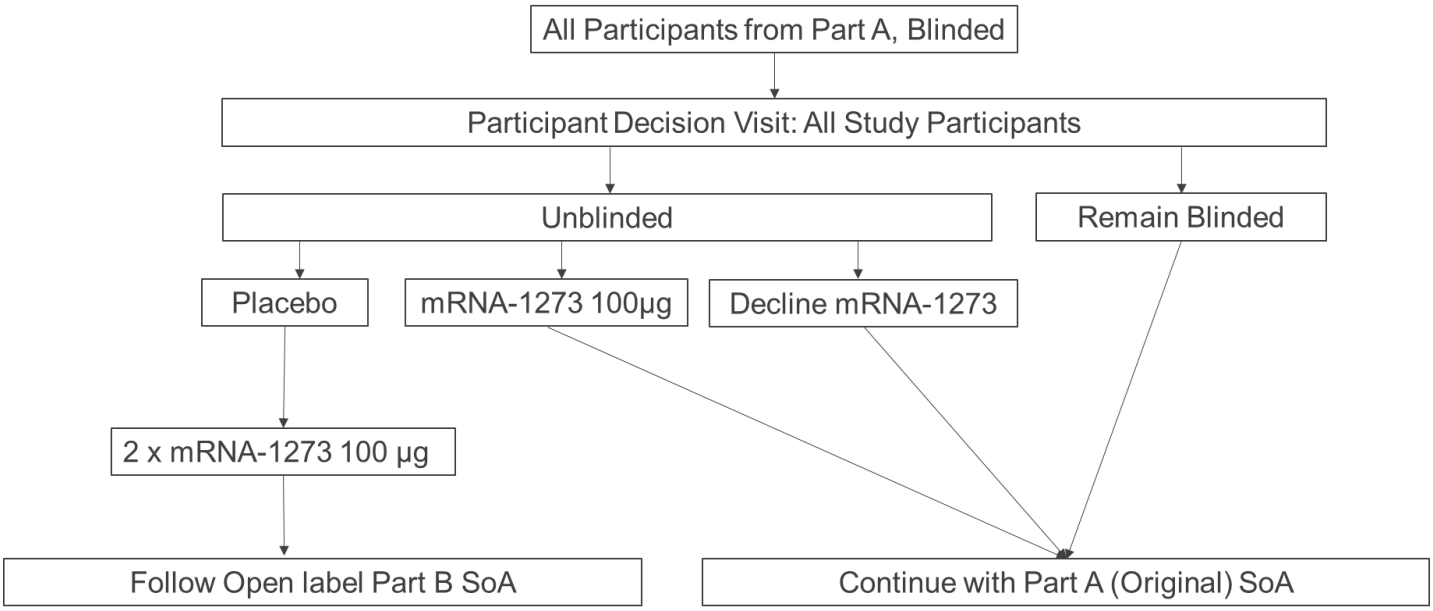
the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms (eCRFs) should be completed for each unscheduled visit.

3.1.2. Part B, the Open-label Observational Phase

Part B, the Open-label Observational Phase of the study, will be prompted by the authorization of a COVID-19 vaccine under an EUA for any persons under the age of 18 years. Participants will be transitioned to Part B of the study as their age group becomes EUA-eligible. This transition permits all ongoing study participants to eventually be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and the option to offer all ongoing study participants an opportunity to schedule a Participant Decision Visit to know their original treatment assignment (placebo vs. mRNA-1273 100 µg vaccine).

Part B provides the opportunity for study participants to be informed regarding the EUA, to be unblinded to their original assignment (mRNA-1273 or placebo), and, for those who previously received placebo, to actively request to receive 2 doses of mRNA-1273 (100 µg) vaccine.

Figure 2: Study Schema (Part B, Open-label Observational Phase)



Abbreviation: SoA = Schedule of Assessments.

At the Participant Decision Clinic Visit (Table 8), EUA-eligible participants will:

- Be given the option to be unblinded as to their original group assignment (placebo vs. mRNA-1273 vaccine [100 µg]),
- Be counseled about the importance of continuing other public health measures to limit the spread of disease including social distancing, wearing a mask, and hand-washing,
- Sign a revised ICF and assent if not signed at a previous clinic visit, and
- Provide an NP swab for RT-PCR for SARS-CoV-2 and a blood sample for serology and immunogenicity.

After the Participant Decision Clinic Visit, participants will follow the Part A SoA (Table 7) or Part B SoA (Table 9) as follows:

- Participants received placebo in Part A and consent to unblinding and to receiving 2 doses of mRNA-1273 in Part B: These participants will proceed to Part B and follow the Part B SoA in

- Table 9.
- Participants received 2 doses of mRNA-1273 in Part A and consent to unblinding: Due to statistical considerations, these participants will be considered as entering Part B (the Open-label Observational Phase) but will continue to follow the Part SoA in Table 7.
- Participants decline unblinding: These participants will remain in Part A and follow the Part A SoA in Table 7.

3.2. Scientific Rationale for Study Design

The single age cohort in this Phase 2/3 study, 12 to < 18 years of age, was established to understand the tolerability and immunogenicity of mRNA-1273 in an adolescent population. The lower age boundary used in this study is consistent with the definition of adolescence provided by the American Academy of Pediatrics (Hardin et al 2017). Knowledge of the tolerability of mRNA-1273 in adolescent participants will be critical before proceeding to future studies in younger children.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre-injection blood samples and postinjection blood samples for Ab analysis through 12 months after the last dose of IP. In addition, participants will have NP swab samples collected, before the injections on Day 1 and Day 29, and on Day 57. Furthermore, with any signs or symptoms or MAAE suggesting SARS-CoV-2 infection in a participant, an additional nasal or NP swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via serology and RT-PCR. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

As it is possible that participants are naturally exposed to SARS-CoV-2 through community exposure, the NP and/or nasal swab samples collected before study injection and the serologic assays for Ab responses to nonvaccine antigen(s) may help discriminate between natural infection and vaccine-induced Ab responses, should such discrimination be needed.

3.3. Justification for Dose, Control Product, and Choice of Study Population

The 100 μg dose level is currently being investigated in a large Phase 3 efficacy study in adults 18 years of age and older; therefore, based on this and the results of the studies described in Section 1.2.2, the Sponsor intends to study a single dose level of 100 μg in this Phase 2/3 study in the adolescents age group of 12 to < 18 years of age.

As there are currently no licensed SARS-CoV-2 vaccines available, 0.9% sodium chloride will be used as a placebo control for the safety and immunogenicity assessments. Consequently, the mRNA-1273 vaccine and placebo injections will look different, so administration will be blinded in Part A of this study (Section 8.1).

Following potential EUA of a COVID-19 vaccine for persons under 18 years of age, this study amendment is designed to give EUA-eligible participants the opportunity to transition to Part B, the Open-label Observational Phase (Figure 2). Transitioning the study to Part B, Open-label Observational Phase, permits (a) all ongoing study participants to be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and (b) the option to offer all ongoing study participants who request unblinding an opportunity to schedule a study visit to know their original group assignment (placebo vs. mRNA-1273 [100 µg vaccine]). Part B, the Open-label Observational Phase, also provides the opportunity for study participants who previously received placebo to request to receive 2 doses of mRNA-1273 (100 µg) vaccine.

3.4. End-of-Study Definition

The end-of-study (EOS) for the full study is defined as completion of the last visit of the last participant in the study or the last scheduled procedure as shown in the Part A SoA (Table 7) for the last participant in this study.

4. STUDY POPULATION (PART A: BLINDED PHASE AND PART B: OPEN LABEL OBSERVATIONAL PHASE)

Participants will be enrolled at approximately 15 to 25 study sites in the United States or its territories.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Eligibility Criteria (Part A)

4.1.1. Inclusion Criteria

Each participant must meet all of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, 12 to < 18 years of age at the time of consent (Screening Visit, Day 0) who, in the opinion of the investigator, is in good general health based on review of medical history and screening physical examination.
2. Investigator assessment that the participant, in the case of an emancipated minor, or parent(s)/legally acceptable representative(s) [LAR(s)] understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures and provides written informed consent/assent.
3. Body mass index (BMI) at or above the third percentile according to WHO Child Growth Standards at the Screening Visit (Day 0); see Section 10.2.18.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche or surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy).
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test at Screening (Day 0), on the day of the first injection (Day 1), and on the day of the second injection (Day 29)
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1)
    - Has agreed to continue adequate contraception or abstinence through 3 months following the second injection (Day 29)

Adequate female contraception is defined as consistent and correct use of a US Food and Drug Administration (FDA)-approved contraceptive method in accordance with the product label (Section 10.3).

4.1.2. Exclusion Criteria

Participants who meet any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Travel outside of the United States in the 28 days prior to the Screening Visit (Day 0).
2. Pregnant or breastfeeding.
3. Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
4. Prior administration of an investigational CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.
5. Current treatment with investigational agents for prophylaxis against COVID-19.
6. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
7. Current use of any inhaled substance (eg, tobacco or cannabis smoke, nicotine vapors).
8. History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).
9. History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of screening.
10. History of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
    - Congenital or acquired immunodeficiency, including human immunodeficiency virus (HIV) infection.
    - Suspected active hepatitis
    - Has a bleeding disorder that is considered a contraindication to IM injection or phlebotomy

- Dermatologic conditions that could affect local solicited AR assessments
- History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine
- Diagnosis of malignancy within the previous 10 years (excluding nonmelanoma skin cancer)
- Febrile seizures

11. Receipt of:
    - Any licensed vaccine within 28 days before the first dose of IP or plans for receipt of any licensed vaccine through 28 days following the last dose of IP
    - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 20 mg/day prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the day of enrollment. Participants may have visits rescheduled for enrollment if they no longer meet this criterion within the Screening Visit window. Inhaled, nasal, and topical steroids are allowed.
    - Intravenous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrollment
12. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.
13. Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.
14. Is an immediate family member or has a household contact who is an employee of the research center or otherwise involved with the conduct of the study.

4.2. Study Eligibility Criteria (Part B)

1. Participants must have been previously enrolled in the mRNA-1273 P203 study.
2. Female participants of childbearing potential may be enrolled in the study if the participant has a negative pregnancy test on the day of the first injection (OL-Day 1) and on the day of the second injection (OL-Day 29).

4.3. Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

4.4. Screen Failures (Part A: Blinded Phase Only)

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to treatment. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimum information includes date of informed consent, demography, reason(s) for screen failure, eligibility criteria, and information on any SAE that may have occurred from Day 1 to the time of withdrawal.

5. STUDY TREATMENT

5.1. Investigational Product Administered

The term IP refers to mRNA-1273 (100 μg) vaccine or placebo (0.9% sodium chloride) in this study.

The mRNA-1273 is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000 [PEG2000-DMG]). mRNA-1273 injection is provided as a sterile liquid for injection, white to off-white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

5.2. Randomization

Random assignment of participants will use a centralized interactive response technology, in accordance with pregenerated randomization schedules.

5.3. Dosing and Management of mRNA-1273 Vaccine

5.3.1. Preparation of Study Vaccine for Injection

Each dose of IP will be prepared for each participant based on the assigned treatment, as detailed in the mRNA-1273-P203 Pharmacy Manual. The volume of IP injected will be 0.5 mL consisting of either 100 μg dose of mRNA-1273 or placebo (normal saline), as detailed in the mRNA-1273-P203 Pharmacy Manual.

5.3.2. Administration of Study Vaccine

In the Blinded Phase, Part A of the study, each participant will receive 2 doses of IP by IM injection, 28 days apart (ie, Day 1 and Day 29) into the deltoid muscle, according to their assigned regimen and according to the procedures specified in the mRNA-1273-P203 Pharmacy Manual. Preferably, both doses should be administered into the nondominant arm.

In the open-label Part B of the study, mRNA-1273 vaccine will be administered as an IM injection into the deltoid muscle following the injection schedule for each group based on the product received in Part A. Patients who received placebo in Part A will receive 2 doses of mRNA-1273 (100 μg) on open-label (OL) – Day 1 and OL-Day 29 of Part B (Table 9).

At each visit when IP is administered, participants will be monitored for a minimum of 30 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions (SoA, Table 7 and Table 9).

Eligibility for a subsequent dose of IP will be determined by following the criteria outlined in Section 6.

The study sites will be appropriately staffed with individuals with basic cardiopulmonary resuscitation training/certification. Either on-site resuscitation equipment and personnel or appropriate protocols for the rapid transport of participant to a resuscitation area or facility are required.

5.3.3. Study Vaccine Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the IP
- Confirming the appropriate labeling of the IP, so that it complies with the legal requirements of the United States

The investigator is responsible for acknowledging the receipt of the IP by a designated staff member at the study site, including the following:

- Confirming that the IP was received in good condition
- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming that the Sponsor has authorized the IP for use
- Ensuring the appropriate dose level of IP is properly prepared using aseptic technique

Further description of the IP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the IP are described in the mRNA-1273-P203 Pharmacy Manual.

5.3.4. Study Vaccine Packaging and Labeling

The Sponsor will provide the investigator (via the study site pharmacy) with adequate quantities of IP. The sterile IP is packaged in 10R glass vials with a 5.0-mL fill volume. The IP will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

The IP will be packaged and labeled in accordance with the standard operating procedures of the Sponsor or of its designee, Code of Federal Regulations (CFR) Title 21, Good Manufacturing Practice guidelines, International Council for Harmonisation (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

5.3.5. Study Vaccine Storage

The IP must be stored at 2°C to 8°C in a secure area with limited access and protected from moisture and light until it is prepared for administration (Section 5.3.1). The refrigerator should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. There must be an available backup refrigerator. The refrigerators must be connected to a backup generator. In addition, IP accountability study staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The study site is responsible for reporting any IP that was not temperature controlled during shipment or during storage. Such IP will be retained for inspection by the monitor and disposed of according to approved methods.

5.3.6. Study Vaccine Accountability

It is the investigator's responsibility that the IP accountability study staff maintain accurate records in an IP accountability log of receipt of all IP, study site IP inventory, IP dispensing, IP injections, and return to the Sponsor or alternative disposition of used and unused IP vials.

A study site monitor will review the inventory and accountability log during study site visits and at the completion of the study. Additional details are found in the mRNA-1273-P203 Pharmacy Manual.

5.3.7. Study Vaccine Handling and Disposal

A study site monitor will reconcile the IP inventory during the conduct and at the end of the study for compliance. Once fully reconciled at the study site at the end of the study, the IP can be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

Vaccine may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A certificate of destruction must be completed and sent to the Sponsor or designee.

5.4. Study Treatment Compliance

All doses of IP will be administered at the study site under direct observation of medically qualified study staff and appropriately recorded (date and time) in the eCRF. Qualified study site staff will confirm that the participant has received the entire dose of IP. If a participant does not receive IP or does not receive all of the planned dose, the reason for the missed dose will be recorded. Data will be reconciled with study site accountability records to assess compliance.

Participants who miss the second dose due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the original visit and testing schedule as described in the protocol and their regimen schedule. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose will remain in the study and complete all

safety and immunogenicity assessments required through the participant's last scheduled study visit.

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (Part A, Table 7 and Part B, Table 9). If a participant does not complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

5.5. Prior and Concomitant Medications

5.5.1. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent/assent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

5.5.2. Concomitant Medications and Therapies

At each study visit, study site staff must question the participant and/or the participants' parent(s)/LAR(s) regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All nonstudy vaccinations administered within the period starting 28 days before the first dose of IP.
- All concomitant medications and nonstudy vaccinations taken through 28 days after each dose of IP. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications relevant to or for the treatment of an SAE or an MAAE.
- Participants will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each dose of IP, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the postinjection study visits or via other participant interactions (eg, telephone calls).

5.5.3. Recording of Concomitant Medications and Concomitant Vaccinations

Study site staff must question the participant regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All nonstudy vaccinations administered within the period starting 28 days before the first dose of IP.
- Seasonal influenza vaccine administered for the current influenza season (typically October through April in the Northern Hemisphere).
- All concomitant medications and nonstudy vaccinations taken through 28 days after each dose of IP. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications used to prevent or treat COVID-19 or its symptoms.
- Any concomitant medications relevant to or for the treatment of an SAE or an MAAE.
- Participants will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each IP dose, including on the day of dosing. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the postinjection study visits or via other participant interactions (eg, phone calls).

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (CRO's) medical monitor will make a joint decision about continuing or withholding further injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

5.5.4. Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol (PP) analysis (analysis sets are described in Section 8.4):

- Any investigational or nonregistered product (drug or vaccine) other than the IP used during the study period.

- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 20 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- Immunoglobulins and/or any blood products administered during the study period.

5.6. Intervention After the End of the Study

Any SAE occurring after the end of the study and considered to be caused by the IP must be reported to the Sponsor.

6. DELAYING OR DISCONTINUING STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

6.1. Criteria for Delay of Vaccine Administration

6.1.1. Individual Participant Criteria for Delay of Study Vaccination

Body temperature (oral) must be measured on dosing visits before vaccine administration. The following events constitute criteria for delay of injection, and if either of these events occur at the time scheduled for dosing, the participant may receive the study injection at a later date within the time window specified in the relevant SoA (Table 7), or the participant may be discontinued from dosing at the discretion of the investigator (Section 6.2):

- Acute moderate or severe infection with or without fever at the time of dosing
- Fever, defined as body temperature ≥ 38.0°C/≥ 100.4°F at the time of dosing

Participants with a minor illness without fever, as assessed by the investigator, can be vaccinated. Participants with a fever of ≥ 38.0°C/≥ 100.4°F will be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the investigator determines that the participant's health on the day of dosing temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit.

If a participant takes a prohibited drug therapy, an injection could be delayed within the visit window based on the joint decision of the investigator and the CRO's medical monitor (Section 5.5.3).

6.2. Discontinuing Study Vaccination

Participants can discontinue study injection (ie, refuse the second dose) for any reason, without prejudice to further treatment the participant may need to receive.

The investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from further injection if the participant experiences any of the following:

- Becomes pregnant
- Withdrawal of consent (not related to COVID-19)
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria (Section 4.1.2)
- Experiences an AE (other than reactogenicity) after injection that is considered by the investigator to be related to IP (Section 7.4.9) and is of Grade 3 (severe) or greater severity

- Experiences an AE or SAE that, in the judgment of the investigator, requires IP withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to vaccine
- Experiences an AESI (MIS-C)
- Experiences a clinically significant change in vital sign measurements, or general condition that, in the judgment of the investigator, requires vaccine withdrawal
- Experiences anaphylaxis clearly related to IP
- Experiences generalized urticaria related to IP

The reason(s) for withdrawal from further injection will be recorded in the eCRF.

If a participant takes a prohibited drug therapy, the investigator could withhold the second dose based on a joint decision of the investigator and the CRO's medical monitor (Section 5.5.3).

Every reasonable attempt will be made to follow up with participants for safety throughout the entire scheduled study period according to their regimen, even if the participant does not receive the second dose or misses one or more visits. Unless participants withdraw consent, they are expected to remain in the study and complete all scheduled visits and assessments.

6.3. Participant Discontinuation/Withdrawal from the Study

Participants who withdraw or are withdrawn from the study will not be replaced. A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol. The statistical management of participant withdrawals is discussed in Section 8.

Participants can withdraw consent and withdraw from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive. The investigator will request that the participant complete all study procedures pending at the time of withdrawal.

If participant desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant until the event is considered resolved or stable and will then complete the EOS eCRF.

Information related to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a participant from the study was made by the participant or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE (specify)
- SAE (specify)
- Death

- Lost to follow-up (LTFU)
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

Participants who are withdrawn from the study because of AEs (including SAEs) must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow up with participants who are withdrawn from the study as result of an SAE or AE until resolution of the event.

A participant who withdraws from the study may request destruction of any samples taken and not tested, and the investigator must document this in the study site study records.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent (Section 10.2.10).

The Sponsor will continue to retain and use all research data that have already been collected for the study evaluation, unless the participant has requested destruction of these samples. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

6.4. Study Pause Rules

During Part A of the study, the investigators, study medical monitor, and Sponsor will monitor for events that could trigger a study pause. Study pause rule criteria, events, and thresholds are described in Table 2. Although these pause rules are not applicable during Part B, participants will continue to be monitored for the events in Table 2, and the Sponsor will be notified if any of these events occur.

Table 2: Pause Rule Criteria, Events, and Thresholds

Pause Rule Criterion	Event	Participant Threshold for Triggering Study Pause
1	Any death due to SARS-CoV-2 infection	≥ 1
2	Any related SAE or related Grade 4 AE	≥ 1
3	Hospitalization due to SARS-CoV-2 infection	≥ 1
4[a]	Any Grade 3 or higher solicited local AR lasting ≥ 24 hours and occurring within 7-days of injection (Days 1-8)	≥ 30 participants out of the first 300 participants enrolled
5[a]	Any Grade 3 or higher solicited systemic AR lasting ≥ 24 hours and occurring within 7-days of injection (Days 1-8)	≥ 30 participants out of the first 300 participants enrolled
6[a]	Any ≥ Grade 3 or higher unsolicited AR that cannot be reasonably attributed to a cause other than vaccination	≥ 30 participants out of the first 300 participants enrolled

Abbreviations: AE = adverse event; AR = adverse reaction; ICU = intensive care unit; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus.
[a.] Pause Rules 4, 5, and 6 apply only to the first 300 participants enrolled.

If any of the thresholds for a study pause is met during Part A, the Sponsor will immediately suspend further enrollment, pause study dosing, and notify all investigators. Such a suspension will remain in force until the threshold event(s) is (are) reviewed by the Data Safety Monitoring Board (DSMB) and a recommendation to continue is provided to the Sponsor.

The investigator or designee is responsible for reporting to the Sponsor, via the electronic data capture (EDC) system within 24 hours of observation, each event that potentially meets any pause rule criterion. The Sponsor will inform the DSMB of any event that potentially meets any pause rule criterion. The DSMB will review all available study data to adjudicate such events in accordance with the DSMB charter.

The Sponsor will notify the Center for Biologics and Evaluation Research (CBER) within 48 hours in the event of a study pause. In the event of a study pause, all safety and immunogenicity assessments will continue per protocol (PP). The window allowance for injection visits may be extended by an additional 7 days (ie, +14 days) for affected participants at the discretion of the Sponsor.

During Part B of the study, the Sponsor will continue to inform the DSMB of the occurrence of any of the events in Table 2. The DSMB will review all available relevant study data to adjudicate such events in accordance with the DSMB charter.

6.5. Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site. The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site staff must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's medical record.
- A participant who continues to be unreachable or continues to be noncompliant with study visits or procedures will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed.

7. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants and/or participants' parent/LAR will sign an ICF (as detailed in Section 10.2.6). Participants will undergo study procedures at the time points specified in the Part A SoA (Table 7).

After the participant proceeds to the Participant Decision Clinic Visit (Part A) of the study, participants who received mRNA-1273 in Part A will continue to follow the open-label Part A SoA (Table 7). Participants who received placebo in Part A will transition to the open-label Part B of the study (Figure 4) and will follow the Part B SoA (Table 9) through OL-Day 57. At this point, Part B participants will return to open-label Part A SoA (Table 7) until study completion.

A participant can also be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. The study site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in Table 7 and Table 9. Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue study treatment or participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline assessments provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

7.1. Safety Assessments and Procedures

In both Part A (blinded) and Part B (open-label), safety assessments will include monitoring and recording of the following for each participant, according to the SoA (Table 7 and Table 9):

- Solicited local and systemic ARs (Section 7.4.3) that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days) in Part A. Solicited ARs will be recorded daily using eDiaries (Section 7.1.1).
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 7.4.1.
- AEs leading to discontinuation from dosing and/or withdrawal from study participation from Day 1 through the last day of study participation (ie, Day 394 per Part A SoA and OL-Month 7 in Part B).
- MAAEs from first dose on Day 1 through the entire study period (ie, Day 394 per Part A SoA and OL-Month 7 in Part B).
- SAEs from first dose on Day 1 through the entire study period (ie, Day 394 per Part A SoA and OL-Month 7 in Part B).
- AESI of MIS-C through the entire study period (ie, Day 394 per Part A SoA and OL-Month 7 in Part B).
- Vital sign measurements (Section 7.1.4)
- Physical examination findings (Section 7.1.5).
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 7.1.6).
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study (Section 7.4.6).

7.1.1. Use of Electronic Diaries

At the time of consent/assent, participants or their caregivers must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. Before enrollment on Day 1, participants or their caregivers will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 7.4.3) on Day 1. Participants who were originally randomized to placebo and who opt to receive mRNA-1273 will enter the Open-label Observational Phase. They will receive Dose 1 at D209 (OL-D1), return for their second dose at

OL-D29, and return again at OL-D57, after which time they will return to the Part A SoA in the safety reporting period. During the open-label period, the eDiary will not be used.

At each injection visit, participants or their caregivers will be instructed (Day 1) or reminded (Day 29) on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

At each injection visit, participants or their caregivers will record data into the eDiary starting approximately 30 minutes after injection under supervision of the study site staff to ensure successful entry of assessments. The study site staff will perform any retraining as necessary. Participants or their caregivers will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection.

Participants or their caregivers will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 7.4.3, that occur on the day of each vaccine administration and during the 7 days after vaccine administration (ie, the day of injection and 6 subsequent days). If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until it is resolves or the next IP injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination and not to exceed 28 days after each vaccination, whichever occurs first. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.
- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurement, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- Any medications taken to treat or prevent pain or fever on a day of injection or for the next 6 days.

The eDiary will be the only source documents allowed for solicited systemic or local ARs (including body temperature measurements). Participants or their caregivers will be instructed to

complete eDiary entries daily. The participant or their caregiver will have a limited window on the following day to complete assessments for the previous day; quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of solicited ARs.

Any new safety information reported during safety telephone calls or at study site visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. An event reported in this manner must be described as a solicited event and entered on the solicited AR eCRF.

Study site staff will review eDiary data with participants at visits 7 days after each injection.

The eDiary will also be used every 4 weeks, starting at Day 71 through Day 183 and again starting at Day 223 through Day 363 for participants in Part A and from Day 279 through Day 363 for participants in Part B (per Figure 4), to capture the occurrence of AEs, MAAEs, SAEs, AESI, or AEs leading to withdrawal. As specified in the applicable SoA (Table 7), the eDiary will prompt the participant to complete an eDiary questionnaire that collects the following data:

- Changes in health since last completing the questionnaire or since in contact with the study site
- Known exposure to someone with known COVID-19 or SARS-CoV-2 infection
- Any experience of symptoms of COVID-19
- Any MAAEs or SAEs

If an eDiary record results in identification of relevant safety events according to the study period, or of symptoms of COVID-19, a follow-up safety telephone call will be triggered.

Completion of eDiary questionnaires will alternate with safety telephone calls (Section 7.1.2) as the procedure for safety follow-up approximately every 4 weeks starting at Day 85 through Day 197 and again starting at Day 237 through Day 377 (Part A SoA, Table 7).

7.1.1.1. Ancillary Supplies for Participant Use

Study sites will distribute Sponsor-provided oral thermometers and rulers for use by participants in assessing body temperature and injection site reactions for recording solicited ARs in eDiaries. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

7.1.2. Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained study site personnel. This call will follow a script, which will facilitate the collection of relevant safety information.

Safety telephone calls follow a schedule for each participant as indicated in the Part A SoA (Table 7).

The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AESI, AEs leading to study withdrawal, concomitant medications associated with those events, and any nonstudy vaccinations (Section 7.4.7). In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms. All safety information collected from the telephone contact must be documented in source documents as described by the participant and not documented on the script used for the safety telephone contact. As noted in Section 7.1.1, an unscheduled follow-up safety telephone call may be triggered if an eDiary record results in identification of a relevant safety event.

7.1.3. Safety Laboratory Assessments

No scheduled laboratory assessments for safety are planned. This is based on the absence of clinically significant abnormal laboratory findings in the Phase 1 and Phase 2 studies of mRNA-1273 in adults.

A point-of-care urine pregnancy test will be performed at the Screening Visit (Day 0) and before each vaccine dose. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.

7.1.4. Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the SoA (Table 77). At dosing visits, vital sign measurements will be collected once before injection and at least 30 minutes post injection (before participants are discharged from the study site).

Febrile participants at dosing visits (fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F) may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

When procedures overlap and are scheduled to occur at the same time point, the order of procedures should be vital sign measurements and then the blood collection.

7.1.5. Physical Examinations

A full physical examination, including height and weight, will be performed at scheduled time points as indicated in the Part A and Part B SoAs (Table 7 and Table 9, respectively). The full

examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Body mass index will be calculated at the Screening Visit (Day 0) only.

7.1.6. Assessment for SARS-CoV-2 Infection

Study participants will have NP samples collected for SARS-CoV-2 testing at time points specified in the SoA (Part A, Table 7 and Part B, Table 9).

For both Part A and Part B, a study illness visit or a consultation will be arranged within 72 hours or as soon as possible to collect an NP or nasal swab sample (NP is preferred) to ascertain the presence of SARS-CoV-2 via RT-PCR if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020b)
- Exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

If the participant had known exposure to COVID-19 (eg, exposure to someone with confirmed COVID-19), it will be captured in the COVID-19 exposure form.

If scheduled, the study illness visit may collect additional clinical information, including assessments such as medical history, physical examination, blood sampling for clinical laboratory testing, and nasal, saliva, and/or NP swab sampling for viral PCR (including multiplex PCR for respiratory viruses including SARS-CoV-2) to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. All findings will be recorded in the eCRF.

If participants are confirmed to have SARS-CoV-2 infection, the investigator will notify the participant, and the participant's primary care physician, of the diagnosis. If the study participant does not have a primary care physician, the investigator will assist them to obtain one. The participant will also be instructed on infection prevention measures consistent with local public health guidance.

Any confirmed symptomatic SARS-CoV-2 infection occurring in participants will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days)

after diagnosis (Section 7.3.3). At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.

7.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoA (Part A, Table 7 and Part B, Table 9): The following analytes will be measured:

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays
- Serum bAb levels against SARS-CoV-2 as measured by ligand-binding assay specific to the SARS-CoV-2 S protein
- Serum bAb levels against SARS-CoV-2 nucleocapsid protein as measured by ligand-binding assay specific to the SARS-CoV-2 nucleocapsid protein

Serum collected from all participants will be tested for bAb against SARS-CoV-2 nucleocapsid protein at specified time points. In addition, serum samples from a selected subset of study participants who received mRNA-1273 will be selected for testing of nAb and bAb against the SARS-CoV-2 S protein. Sample aliquots will be designed to ensure that backup samples are available and that vial volumes are likely to be adequate for future testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

Measurement of bAb and nAb levels will be performed in a laboratory designated by the Sponsor.

According to the ICF (Section 10.2.6), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoVs.

The maximum planned volume of blood sampled per participant for immunogenicity assessments in 1 day is 21 mL.

7.3. Efficacy Assessments

7.3.1. Vaccine Effectiveness Assessments

Vaccine effectiveness for adolescents of ages of 12 to < 18 years will be inferred based on serum Ab responses obtained on Day 57 (28 days after the second injection of mRNA-1273). Inference will be based on assessing the adolescent Ab responses against the following:

1. *If available at the time of analysis*, adolescent Ab responses will be assessed against an accepted serum nAb threshold conferring protection against COVID-19.
2. *If an accepted threshold of protection is not available*, adolescent Ab responses will be assessed by establishing noninferiority of the GM value and seroresponse rate of serum nAb from adolescent participants compared with those from young adults enrolled in the ongoing clinical endpoint efficacy trial (Study P301). The statistical parameters to infer effectiveness are described in Section 2.

COVID-19:

To be considered as a case of COVID-19 for the evaluation of the primary efficacy endpoint, the following case definition must be met:

- The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥ 100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- The participant must have at least 1 NP swab or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Severe COVID-19:

To be considered severe COVID-19, the following criteria must be met:

- Confirmed COVID-19 as per the primary efficacy endpoint case definition, plus any of the following:
  - Clinical signs indicative of severe systemic illness, respiratory rates ≥ 30 per minute, heart rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR
  - Respiratory failure or Acute Respiratory Distress Syndrome, (defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
  - Significant acute renal, hepatic, or neurologic dysfunction, OR
  - Admission to an ICU or death.

The secondary case definition of COVID-19 is defined as the following systemic symptoms: fever (temperature > 38ºC/≥ 100.4ºF), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea AND a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.

Death attributed to COVID-19 is defined as any participant who dies during the study with a cause directly attributed to a complication of COVID-19.

SARS-CoV-2 Infection:

- SARS-CoV-2 infection is defined in participants with SARS-CoV-2 negative at baseline:
  - bAb level against SARS-CoV-2 nucleocapsid protein negative at Day 1, which becomes positive post baseline, OR
  - Post-baseline Positive RT-PCR

7.3.2. Surveillance for COVID-19 Symptoms

Surveillance for COVID-19 symptoms will be conducted via biweekly telephone calls or eDiary prompts as specified in Section 7.1.1 and Figure 3; starting after participant enrollment and throughout the study.

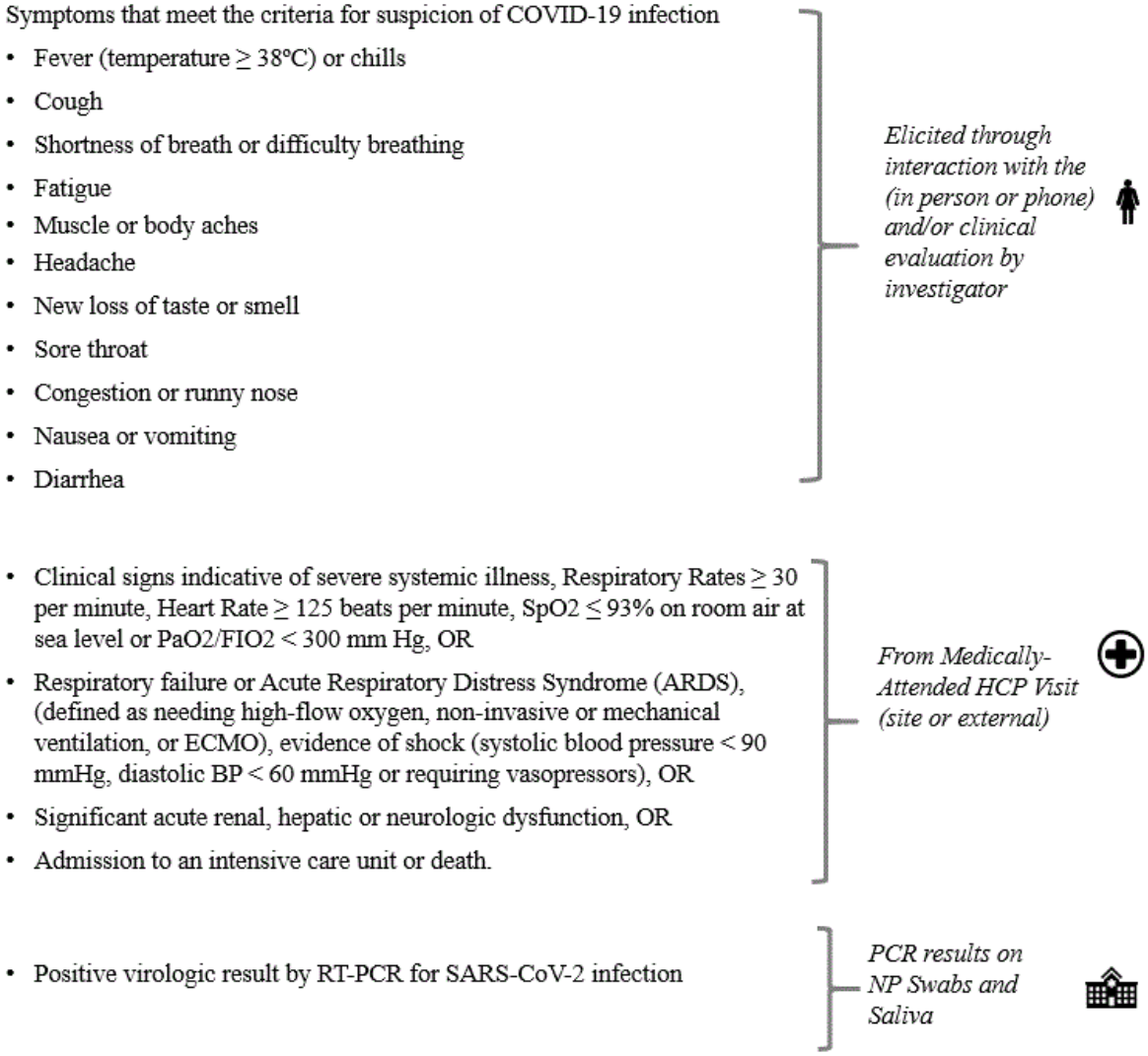
If there is no response to an eDiary prompt for 3 days, the study site staff will contact the study participant by phone.

According to the CDC as of 10 Jun 2020 (CDC 2020c), patients with COVID-19 have reported a wide range of symptoms ranging from mild symptoms to severe illness. Throughout the study, to survey for COVID-19, the following prespecified symptoms that meet the criteria for suspicion of COVID-19 will be elicited weekly from the participant and the presence of any one of these symptoms lasting at least 48 hours (except for fever and/or respiratory symptoms) will result in the study site staff arranging an illness visit to collect an NP swab within 72 hours:

- Fever (temperature ≥ 38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 48 hours)
- Shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours)
- Cough (of any duration, including ≤ 48 hours)
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell

- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

Figure 3: Surveillance for COVID-19 Symptoms and the Corresponding Clinical Data Pathways



Abbreviations: BP = blood pressure, COVID-19 = coronavirus disease 2019, ECMO, SpO2 = oxygen saturation, PaO2 = partial pressure of oxygen, FIO2 = fraction of inspired oxygen, HCP = healthcare practitioner, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

It is important to note that some of the symptoms of COVID-19 overlap with solicited systemic ARs that are expected after vaccination with mRNA-1273 (eg, myalgia, headache, fever, and chills). During the first 7 days after vaccination, when these solicited ARs are common,

investigators should use their clinical judgment to decide if an NP swab should be collected. The collection of an NP swab prior to the Day 1 and Day 29 vaccination can help ensure that cases of COVID-19 are not overlooked. Any study participant who reports respiratory symptoms during the 7-day period after vaccination should be evaluated for COVID-19.

During the course of the study, participants with symptoms of COVID-19 will be asked to return within 72 hours or as soon as possible to the study site or medically qualified staff from the study site will conduct a home visit as soon as possible to collect an NP swab sample (for RT-PCR) for evaluation of COVID-19. Both study site visits and home visits are referred to as illness visits (Section 7.1.6). The NP swab sample will also be tested for the presence of other respiratory infections. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.3). At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection. In addition, the study site may collect an additional respiratory sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care.

Cases are defined as participants meeting clinical criteria based both on symptoms for COVID-19 and on RT-PCR detection of SARS-CoV-2 from samples collected within 72 hours of the study participant reporting symptoms meeting the definition of COVID-19. Participants who are hospitalized for COVID-19 without the opportunity for a clinic or home visit will also be considered cases, assuming that the symptomology criteria for COVID-19 are met and a respiratory sample is positive for SARS-CoV-2 by PCR at a clinical laboratory improvement amendments-certified laboratory. Investigators are encouraged to try to obtain a respiratory sample during the course of hospitalization for submission to the study central laboratory, if feasible. The investigator should determine if the criteria for severe COVID-19 has been met.

Severe COVID-19 is defined in Section 7.3.1.

All clinical findings will be recorded in the eCRF. All confirmed cases of COVID-19 will be captured as MAAEs, along with relevant concomitant medications and details about severity, seriousness, and outcome, and will be reported immediately to the Sponsor or designee (Section 7.4.4).

7.3.3. Follow up/Convalescent Period After Diagnosis with COVID-19

Any confirmed COVID-19 occurring in a participant will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Study participants will be monitored by medically qualified study site personnel for a 28-day period after diagnosis. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection (Table 7). The

investigator should determine if the criteria for severe COVID-19 has been met. If the participant is hospitalized, medically qualified study site personnel will try to obtain medical records and SARS-CoV-2 diagnostic results. If the participant is later discharged from the hospital during the 28-day period following diagnosis of COVID-19, the study site personnel will arrange for a resumption of the protocol schedule.

7.4. Safety Definitions and Related Procedures

7.4.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Events Meeting the Adverse Event Definition

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after the first dose of IP even though they may have been present before the start of the study

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the vaccine caused the AE (Section 7.4.9). For the purposes of investigational new drug safety reporting, “reasonable possibility” means that there is evidence to suggest a causal relationship between the vaccine and the AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (ie, for the 7 days after each dose of vaccine).

7.4.2. Serious Adverse Events

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- **Death**
  A death that occurs during the study or that comes to the attention of the investigator

during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to the IP.

- **Is life-threatening**
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization**
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.
- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly or birth defect**
- **Medically important event**
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.4.3. Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after IP injection. The eDiary will solicit daily participant reporting of ARs using

a structured checklist (Section 7.1.1). Participants will record such occurrences in an eDiary on the day of each dose injection and for the 6 days after the day of dosing.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 3 modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next IP injection occurs whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit. All solicited ARs (local and systemic) will be considered causally related to dosing.

Table 3: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[a]
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[a]
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 - 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 - 104.0°F	> 40.0°C > 104.0°F

[a] Grading for Grade 4 events per investigator assessment (with exception of fever).

Source: Guidance for industry - Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded by the study site staff on the solicited AR page of the participant's eCRF:

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (HCP; otherwise meets the definition of an MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal)
- Solicited local or systemic AR lasting beyond 7 days after injection
- Solicited local or systemic AR that leads to participant withdrawal from IP
- Solicited local or systemic AR that otherwise meets the definition of an SAE

7.4.4. Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (eg, abnormal laboratory test results follow-up, COVID-19 (Section 7.3.1) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAE. All MAAEs must be fully reported on the MAAE page of the eCRF.

All confirmed COVID-19 cases (Section 7.3.1) will be recorded as MAAEs and reported to the Sponsor or designee immediately and in all circumstances within 24 hours, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11). The investigator will submit any updated COVID-19 case data to the Sponsor within 24 hours of it being available.

7.4.4.1. Anaphylaxis

All suspected cases of anaphylaxis should be recorded as MAAEs and reported as SAEs (Section 7.4.2) based on criteria for a medically important event, unless the event meets other serious criteria. As an SAE, the event should be reported to the Sponsor or designee immediately and in all circumstances within 24 hours as per Section 7.4.10 (Reporting SAEs). The investigator will submit any updated anaphylaxis case data to the Sponsor within 24 hours of it being available. For reporting purposes, a participant who displays signs/symptoms consistent with anaphylaxis as shown below should be reported as a potential case of anaphylaxis. This is provided as general guidance for Investigators and is based on the Brighton Collaboration case definition (Rüggeberg et al 2007).

Anaphylaxis is an acute hypersensitivity reaction with multi-organ-system involvement that can present as or rapidly progress to a severe life-threatening reaction. It may occur following exposure to allergens from a variety of sources. Anaphylaxis is a clinical syndrome characterized by:

- Sudden onset AND
- Rapid progression of signs and symptoms AND
- Involving two or more organ systems, as follows:
  - **Skin/mucosal**: urticaria (hives), generalized erythema, angioedema, generalized pruritus with skin rash, generalized prickle sensation, red and itchy eyes
  - **Cardiovascular**: measured hypotension, clinical diagnosis of uncompensated shock, loss of consciousness or decreased level of consciousness, evidence of reduced peripheral circulation
  - **Respiratory**: bilateral wheeze (bronchospasm), difficulty breathing, stridor, upper airway swelling (lip, tongue, throat, uvula, or larynx), respiratory distress, persistent dry cough, hoarse voice, sensation of throat closure, sneezing, rhinorrhea
  - **Gastrointestinal**: diarrhea, abdominal pain, nausea, vomiting

7.4.5. Adverse Events of Special Interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation to characterize and understand them. In this trial, MIS-C is considered an AESI and must be reported to the Sponsor or designee immediately and in all circumstances within 24 hours of becoming aware of the event via the EDC system throughout the entire study period. If a site receives a report of a new AESI from a study participant or receives updated data on a previously reported AESI

and the eCRF has been taken offline, then the site can report this information on a paper AESI form using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11**Error! Reference source not found.**).

Investigators will be asked to report, as AESI, clinical signs/symptoms consistent with the CDC case definition of MIS-C (https://emergency.cdc.gov/han/2020/han00432.asp):

- An individual aged < 21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological);

AND

- No alternative plausible diagnoses;

AND

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms:

    1. Fever ≥ 38.0°C/≥ 100.4ºF for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours
    2. Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin

Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C. Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

All cases of MIS-C will be reported to the Sponsor or designee immediately and in all circumstances within 24 hours, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11).

7.4.6. Recording and Follow-up of Pregnancy

Female individuals who have a positive pregnancy test at Screening should not be enrolled; participants who have a positive pregnancy test any time during the study should receive no further dosing with IP but should be asked to remain in the study and be monitored for safety.

Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the study site learning of its occurrence, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11). If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

7.4.7. Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor.

Solicited ARs will be collected from Day 1 through 7 days after each dose only in Part A. Other (unsolicited) AEs will be collected from Day 1 through 28 days after each dose.

Both MAAEs and SAEs will be collected from participants as specified in the SoA until the end of their participation in the study (ie, Day 394 in Part A and Month 7 in Part B). Any AEs that occur before administration of IP will be analyzed separately from AEs.

At every study site visit or telephone contact, participants will be asked a standard question to elicit any medically related changes in their well-being (including COVID-19 symptoms) according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any nonstudy vaccinations.

In addition to participant observations, physical examination findings, or data relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 6.4).

7.4.8. Assessment of Intensity

An event is defined as "serious" when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 7.4.2), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant's daily activities. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic reactogenicity events (solicited ARs), and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 7.4.3.

The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definitions of severity as follows:

- Mild: These events do not interfere with the participant's daily activities.
- Moderate: These events cause some interference with the participant's daily activities and require limited or no medical intervention.
- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

Study staff should elicit from the participant the impact of AEs on the participant's activities of daily living to assess severity and document appropriately in the participant's source documentation. Changes in the severity of an AE should be documented in the participant's source documentation to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

7.4.9. Assessment of Causality

The investigator's assessment of an AE's relationship to IP is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the IP caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

Not related: There is not a reasonable possibility of a relationship to the IP. Participant did not receive the IP OR temporal sequence of the AE onset relative to administration of the IP is not reasonable OR the AE is more likely explained by another cause than the IP.

Related: There is a reasonable possibility of a relationship to the IP. There is evidence of exposure to the IP. The temporal sequence of the AE onset relative to the administration of the IP is reasonable. The AE is more likely explained by the IP than by another cause.

7.4.10. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to IP or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes the type of event, time of onset, investigator-specified assessment of severity (impact on activities of daily living) and relationship to IP, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

7.4.11. Reporting SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Any AE considered serious by the investigator or that meets SAE criteria (Section 7.4.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE) via the EDC system. The investigator will assess whether there is a reasonable possibility that the IP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline (USA and Canada): +1-866-599-1341

- SAE Fax line (USA and Canada): +1-866-599-1342

Regulatory reporting requirements for SAE are described in Section 7.4.15.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, and remain responsible for following up AEs that are serious, considered related to IP or study procedures, or that caused the participant to discontinue the study.

7.4.12. Time Period and Frequency for Collecting AE and SAE Information

Medical occurrences that begin before the start of IP dosing but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

Adverse events may be collected as follows:

- Observing the participant
- Receiving an unsolicited complaint from the participant
- Questioning the participant in an unbiased and nonleading manner

Solicited ARs will be collected from the day of injection through 6 days after each dose. Other (unsolicited) AEs will be collected from the day of injection through 28 days after each dose.

Serious AEs will be collected from the start of IP dosing until the last day of study participation.

All SAEs will be recorded and reported to the Sponsor or designee immediately and in all circumstances within 24 hours. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the investigator to be clinically significant (eg, leads to dose modification or study drug discontinuation, or meets any serious criteria). If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

Investigators are not obligated to actively seek AEs or SAEs after EOS participation. However, if the investigator learns of any SAE (including a death) at any time after a participant has withdrawn from or completed the study, and the investigator considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the Sponsor.

7.4.13. Method of Detecting AEs and SAEs

Electronic diaries have specifically been designed for this study by the Sponsor. The diaries will include prelisted AEs (solicited ARs) and intensity scales; they will also include blank space for the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations.

The investigator is responsible for the documentation of AEs regardless of treatment group or suspected causal relationship to IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about the occurrence of AE.

7.4.14. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits and contacts.

All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 6.4.

7.4.15. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reaction according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

7.5. Safety Monitoring

The CRO's medical monitor, the Sponsor's medical monitor, and the individual study site investigators will monitor safety throughout the study.

7.5.1. Data Safety Monitoring Board

Safety oversight will be under the direction of a DSMB composed of external independent consultants with relevant expertise. Members of the DSMB will be independent from the study conduct and free of conflict of interest.

The DSMB will have separate meetings by teleconference to review unblinded safety data when half of the study population (1,500 randomized participants) have reached Day 8 (1 week after Dose 1) and again approximately when 25% (750), 50% (1,500), and 75% (2,250) of enrolled participants have reached Day 36 (1 week after Dose 2). Recruitment will continue, as applicable, during the DSMB review period. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. Details regarding the DSMB composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

The DSMB will convene on an ad hoc basis if any of the pause rules, described in Section 6.4, are met. The DSMB will review all available unblinded study data to adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

7.6. Treatment of Overdose

As the study treatment is to be administered by a healthcare professional, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 10.2.8).

7.7. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

7.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

7.9. Biomarkers

Immunogenicity assessments are presented in Section 7.2. Biomarkers are not evaluated in this study.

7.10. Health Economics

Health economics are not evaluated in this study.

8. STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical database lock for the study. If changes are made to primary and/or key secondary objectives and hypotheses or the statistical methods related to those hypotheses after the study has begun but prior to any data unblinding, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or clinical study report (CSR) for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

8.1. Blinding and Responsibility for Analyses

See Section 3.1.1 regarding the addition of a participant decision visit as part of this protocol amendment.

Part A of this study is observer-blind. The investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end or initiation of Part B, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1273 (or placebo) to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of IP to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded study site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that study sites are following all proper IP accountability, preparation, and administration procedures.
- An unblinded statistical and programming team will perform the preplanned interim analyses (IAs, Section 8.6.1). Sponsor team members will be prespecified to be unblinded to the IA results and will not communicate the results of IA to the blinded investigators, study site staff, clinical monitors, or participants. This is detailed in the study Data Blinding Plan.

In Part A, the dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the IP in a secure location that is not accessible or visible to other study staff. An opaque

sleeve over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1273 will look different to that of placebo. Only delegated unblinded study site staff will conduct the injection procedure. Once the injection is completed, only the blinded study staff will perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

A limited number of Sponsor and CRO personnel will be unblinded for:

- The safety interim analysis in participants who are 16-17 years of age after approximately 250 participants in this age group have completed the Day 57 visit in Part A.
- The interim analysis of immunogenicity and safety that will be performed when participants in an Immunogenicity Subset or all participants have reached Day 57 in Part A, including all required samples for immunogenicity testing to support the primary immunogenicity analysis.

The purpose of the unblinding is to enable the group to develop regulatory submission documents and to address questions from regulatory agencies during the regulatory review of the submission. After unblinding, this unblinded team will not participate in the conduct or execution of the subsequent course of the study. The study Data Blinding Plan provides details of the blinding/unblinding process and personnel. The study site staff, investigators, study monitors, and participants will remain blinded until the initiation of Part B.

8.1.1. Breaking the Blind

A participant or participants may be unblinded in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for interim analyses as outlined in Section 8.6.1.

8.2. Statistical Hypothesis

If an accepted serum Ab threshold of protection against COVID-19 is established for the primary immunogenicity objective, the null hypothesis is that the percentage of participants on

mRNA-1273 with serum Ab equal to or above the established threshold at Day 57 is ≤ 70% (ie, H_0: percentage of participants on mRNA-1273 ≤ 70% with serum Ab at Day 57 equal to or above the established threshold).

The study would be considered as meeting the immunogenicity objective if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 70% (lower bound of the 95% CI > 70%).

If an accepted serum Ab threshold of protection against COVID-19 is not available for the primary immunogenicity objective, the immunogenicity analysis of primary vaccine response will be performed using the noninferiority tests of the two null hypotheses based on the two coprimary endpoints, respectively.

Coprimary endpoint 1: Ab GM at Day 57

The null hypothesis:

H^1_0: immunogenicity response to mRNA-1273 as measured by Ab GM at Day 57 is inferior in adolescents (12 to < 18 years of age) compared with that in young adults (18-25 years of age) using mRNA-1273 Study P301 data.

The noninferiority in Ab GM in adolescents compared with that in young adults (18-25 years of age) is demonstrated by that the lower bound of the 95% CI of the geometric mean ratio (GMR) rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5. The GMR is the ratio of the GM value of adolescents on mRNA-1273 in this study, Study P203, at Day 57 compared with the GM value of young adults (18-25 years of age) on mRNA-1273 in Study P301.

Coprimary endpoint 2: Ab seroresponse rate at Day 57

A definition of seroresponse will be provided in the SAP based on forthcoming information about assay performance.

The null hypothesis:

H^2_0: immunogenicity response to mRNA-1273 as measured by seroresponse rate at Day 57 is inferior in adolescents (12 to < 18 years of age) compared with that in young adults (18-25 years of age) using mRNA-1273 Study P301 data.

The noninferiority in seroresponse rate in adolescents compared with that in young adults (18-25 years of age) is demonstrated by that the lower bound of the 95% CI of the seroresponse rate difference rules out -10% (ie, lower bound > -10%) using the noninferiority margin of 10%. The seroresponse rate difference is defined as the rate in adolescents receiving mRNA-1273 minus the rate in young adults (18-25 years of age) receiving mRNA-1273 from Study P301.

The study would be considered as meeting the primary immunogenicity objective if noninferiority is demonstrated based on both coprimary endpoints.

Details regarding the assay to be used to assess noninferiority will be provided in the SAP.

8.3. Power and Sample Size

The sample size of this study is driven by safety. Approximately 3,000 participants will be randomly assigned in a 2:1 ratio to receive mRNA-1273 and placebo (Section 5.2). With 2,000 participants exposed to mRNA-1273, the study has at least 90% probability to observe at least 1 participant with an AE at a true 0.25% AE rate.

Serum samples from all participants will be collected and banked, a subset of participants will be selected, and their samples will be processed for immunogenicity testing (the Immunogenicity Subset).

Approximately 362 participants who receive mRNA-1273 will be selected for the Immunogenicity Subset, with a target of 289 participants receiving mRNA-1273 in the PP Immunogenicity Subset (adjusting for approximately 20% of participants who may be excluded from the PP Immunogenicity Subset, as they may not have immunogenicity results due to any reason). The sample size of the Immunogenicity Subset may be updated with data from other mRNA-1273 studies or external data especially regarding a threshold of protection. In such a situation, the final sample size of the Immunogenicity Subset will be documented in the SAP.

For the primary immunogenicity objective, with approximately 289 participants in the PP Immunogenicity Subset, the study will have > 90% power to rule out 70% with a 2-sided 95% CI for the percentage of mRNA-1273 participants exceeding the acceptable threshold if the true rate of participants exceeding the acceptable threshold is 80%.

If an acceptable Ab threshold of protection against COVID-19 is not available at the time of analysis, for the primary immunogenicity objective, noninferiority tests of two null hypotheses based on two coprimary endpoints, respectively, will be performed. The sample size calculation for each of the two noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants in the PP Immunogenicity Subset in Study P203 and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) from Study P301, there will be 90% power to demonstrate noninferiority of the immune response as measured by Ab GM in adolescents in Study P203 at a 2-sided alpha of 0.05, compared with that in young adults (18-25 years of age) from Study P301 receiving mRNA-1273, assuming an underlying geometric mean ratio (GMR) value of 1 and a

noninferiority margin of 1.5. The standard deviation (SD) of the log-transformed levels is assumed to be 1.5.

- With approximately 289 participants in the PP Immunogenicity Subset in Study P203 and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) from Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by the seroresponse rate in adolescents in Study P203 at a 2-sided alpha of 0.05, compared with that in young adults (18-25 years of age) from Study P301 receiving mRNA-1273, assuming a true seroresponse rate of 85% in young adults (18-25 years of age) from Study P301, and a true seroresponse rate of 85% in adolescents in Study P203 (ie, true rate difference is 0 compared to young adults from Study P301), and a noninferiority margin of 10%.

8.4. Analysis Sets

The analysis sets are defined in Table 4.

Table 4: Analysis Sets

Analysis Set	Description
Randomization Set	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received at least 1 injection of IP.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing.
Per-protocol (PP) Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset who received planned doses of study vaccination per schedule, complied with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. Participants who are seropositive at baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for analyses of immunogenicity unless specified otherwise.
PP Set for Efficacy	All participants in the FAS who received planned doses of study vaccination, had no immunologic or virologic evidence of prior COVID-19, and have no major protocol deviations that impact key or critical efficacy data.
Solicited Safety Set	The Solicited Safety Set consists of FAS participants who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Safety Set	All randomized participants who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for the solicited ARs.
Modified Intent-to-Treat (mITT) Set	All participants in the FAS who have no serologic or virologic evidence of prior SARS-CoV-2 infection before the first dose of IP (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) at baseline
Modified Intent-to-Treat-1 (mITT1) Set	All participants in the mITT Set excluding those who received the wrong treatment (ie, at least 1 dose received in Part A is not as randomized).

Abbreviations: AR = adverse reaction; bAb = binding antibody; COVID 19 = coronavirus disease 2019; FAS = full analysis set; IP = investigational product; mITT = modified intent-to-treat; PP = per protocol; RT-PCR = reverse transcription polymerase chain reaction.

8.5. Statistical Methods

Data from Part A and Part B will be presented separately as applicable.

8.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, race, sex, height, weight, and BMI) and baseline characteristics will be summarized by treatment group. Summary statistics (mean, SD for continuous variables, and number and percentage for categorical variables) will be provided.

8.5.2. Safety Analyses

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by treatment group.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to discontinuation, vital sign measurements, and physical examination findings.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be summarized.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each dose will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from IP or withdrawal from the study will be summarized. Unsolicited AEs will be presented by MedDRA preferred term and system organ class.

The number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided, and Table 5 summarizes analysis strategy for safety parameters. Further details will be described in the SAP.

Table 5: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any solicited AR (overall and by local, systemic)	X	X
Any unsolicited AE	X	—
Any SAE	X	—
Any unsolicited MAAE	X	—
Any unsolicited treatment-related AE	X	—
Any treatment-related SAE	X	—
Discontinuation due to AE	X	—
Any severe AE	X	—
Any treatment-related severe AE	X	—

Abbreviations: AE = adverse event; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by SOC and PT coded by MedDRA.

8.5.3. Immunogenicity Analyses

The SAP will describe the complete set of immunogenicity analyses, including the approach to sample participants into an Immunogenicity Subset for analysis of immunogenicity. The PP Immunogenicity Subset is the primary analysis set for immunogenicity unless otherwise specified. The primary immunogenicity objective of this study is to use the immunogenicity response to infer efficacy in adolescents (12 to < 18 years in this study).

If an accepted serum Ab threshold of protection against COVID-19 is available based on data from other mRNA-1273 studies or external data, the number and percentage of participants with Ab greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. If the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity objective of this study will be considered to be met.

The percentage of participants with serum Ab greater than or equal to the threshold with 95% CI will be provided at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum Ab threshold of protection against COVID-19 is not established, the noninferiority of primary vaccine response as measured by Ab GM and seroresponse rate in adolescents compared with those in young adults (18-25 years of age) receiving mRNA-1273 will be assessed. The study is considered as meeting the primary immunogenicity objective if the noninferiority of the immune response to mRNA-1273 as measured by both GM and seroresponse rate at Day 57 is demonstrated in adolescents in this study at a 2-sided alpha of 0.05, compared with that in young adults (18-25 years of age) in Study P301 receiving mRNA-1273.

An analysis of covariance (ANCOVA) model will be carried out with Ab value at Day 57 as a dependent variable and a group variable (adolescents in Study P203 and young adults in Study P301) as the fixed variable. The GM values of the adolescents at Day 57 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. A corresponding 2-sided 95% CI will be provided to assess the difference in immune response for the adolescents in Study P203 compared to the young adults (18-25 years of age) in Study P301 at Day 57. The noninferiority of immune response to mRNA-1273 as measured by GM will be considered demonstrated if the lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5.

The number and percentage (rate) of participants achieving Ab seroresponse at Day 57 will be summarized. The difference of seroresponse rates between adolescents receiving mRNA-1273 in Study P203 and young adults (18-25 years of age) receiving mRNA-1273 in Study P301 will be calculated with 95% CI. The noninferiority in seroresponse rate of adolescents in Study P203 compared to young adults (18-25 years of age) in Study P301 will be considered demonstrated if the lower bound of the 95% of the seroresponse rate difference is > -10%, based on the noninferiority margin of 10%.

In addition, the GM level of specific nAb and bAb with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log transformed values then back transformed to the original scale. The geometric mean fold-rise (GMFR) of nAb and bAb with corresponding 95% CI will be provided at each time point with Day 57 as the primary time point of interest. Descriptive summary statistics including median, minimum, and maximum will also be provided.

8.5.4. Efficacy Analyses

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate will be provided by vaccination group, calculated as the number of cases divided by the total person-time. The incidence rate ratio of mRNA-1273 versus placebo may be provided with its 95% CI computed using the exact method conditional upon the total number of cases adjusted by the total person-time.

For SARS-CoV-2 infection (serologically confirmed SARS-CoV-2 infection or COVID-19), regardless of symptomatology or severity, infection rate will be provided by vaccination group. The infection rate ratio of mRNA-1273 versus placebo may be provided with its 95% CI using the exact method conditional upon the total number of cases adjusted by the total person-time. The incidence rate of asymptomatic SARS-CoV-2 infection will also be provided.

The secondary efficacy analyses will be performed in the PP set, with sensitivity analyses in the FAS, mITT Set, and mITT1 Set.

8.5.5. Long-term Analysis

Long-term analysis will be performed including data collected in the Open-label Observational Phase (Part B). Long-term analysis of applicable safety, efficacy, and immunogenicity endpoints will be summarized descriptively by treatment cohort as defined in Table 6 without treatment group comparison.

In the long-term safety analysis, unsolicited AEs (SAE, MAAE, and AE leading to discontinuation) and deaths will be summarized.

In the long-term immunogenicity analysis, nAb and bAb values will be summarized at specified timepoints.

In the long-term efficacy analysis, the incidence rates of COVID-19 and of SARS-CoV-2 infection cases will be counted starting 14 days after the second dose of IP for participants in treatment cohorts of mRNA-1273 and Placebo or starting 14 days after the second dose of mRNA-1273 for participants in the Placebo-mRNA-1273 cohort. Incidence rate with 95% CI adjusting for person-time will be provided. The incidence rate of asymptomatic SARS-CoV-2 infection will also be provided.

Table 6: Treatment Cohorts for the Long-term Analysis

Treatment Cohort	Description
mRNA-1273	Participants randomized to mRNA-1273 in the Blinded Phase
Placebo	Participants randomized to Placebo in the Blinded Phase who do not cross over to mRNA-1273 in the Open-label Observational Phase
Placebo-mRNA-1273	Participants randomized to Placebo in the Blinded Phase who cross over to mRNA-1273 in the Open-label Observational Phase

8.5.6. Exploratory Analyses

Exploratory analyses will be described in the SAP before database lock.

8.5.7. Subgroup Analyses

Subgroup analyses will be performed as described in the SAP.

8.6. Study Analyses

8.6.1. Interim Analyses

More than one interim analysis will be performed.

- The first interim analysis of safety in this study will be performed when approximately 250 participants 16-17 years of age have completed Day 57 (1 month after Dose 2, Part A).
- The interim analysis of immunogenicity and safety data will be performed after participants in an Immunogenicity Subset and a subset of all participants have completed Day 57 study procedures (in Part A), including all required immunogenicity data for the primary immunogenicity analysis. This interim analysis will be considered the primary analysis of immunogenicity. At the Sponsor's discretion, a CSR may be developed for the interim analysis.

8.6.2. Final Analysis

The final analysis of all applicable endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in a final CSR, including individual listings.

Additional information about all study analyses may be provided in the SAP.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: Schedule of Assessments

The schedules of assessments are presented in Table 7 for Part A, and

Table 9 for Part B.

If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Screening or Day 1, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor (Section 7). If neither a participant visit to the study site nor a home visit to the participant is possible (with the aforementioned exceptions), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls.

After the Participant Decision Clinic Visit, participants will follow the Part A SoA (Table 7) or Part B SoA (Table 9) with a return to the Part A SOA after Day OL-57, as described in Section 3.1.2 and as shown in Figure 4.

Table 7: Schedule of Assessments Part A, Blinded Phase; Part B Open-Label Observational Phase for Participants who Received mRNA-1273 in Part A

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209/ Participant Decision Visit[3,6]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	±3	± 3	- 28/+ 56	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Informed consent/assent form, demographics, concomitant medications, medical history	X											
Revised informed consent/assent form									X			
Review of inclusion and exclusion criteria	X	X										
Physical examination including vital signs, height, weight[7]	X	X		X		X			X			X
Pregnancy test[8]	X	X		X								
Randomization		X										
Study injection (including 30-minute postdose observation period)		X		X								

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209/ Participant Decision Visit[3,6]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	±3	± 3	- 28/+ 56	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Blood sample for vaccine immunogenicity[9]		X				X			X			X
Nasopharyngeal swab sample for SARS-CoV-2[10]		X		X		X			X			
Surveillance for COVID-19/ Illness visit[11]/ Unscheduled visit		X	X	X	X	X	X	X	X	X	X	X
Convalescent Visit[12]		X	X	X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[13]		X		X								
Review of eDiary data			X		X							
Follow-up safety telephone calls[14]								X		X		
Recording of unsolicited AEs		X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[15]		X	X	X	X	X	X		X	X		X

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209/ Participant Decision Visit[3,6]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	±3	± 3	- 28/+ 56	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[15]		X	X	X	X	X	X		X	X		X
Recording of AESI (MIS-C)		X	X	X	X	X	X		X	X		X
Recording of concomitant medications and non-study vaccinations[15]		X	X	X	X	X						
Study completion												X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; FDA = US Food and Drug Administration; ICF = informed consent form; IRB = institutional review board; M = month; MAAE = medically attended AE; MIS-C = multisystem inflammatory syndrome of children; SC = safety (telephone) call; SFU = safety follow-up; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (DHHS 2020), investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor.

Note: If during the participant decision visit (Table 8) the participant is unblinded and determined to have received 2 doses of mRNA-1273 in Part A, due to statistical considerations, they will be considered as entering Part B (the Open-label Observational Phase) but will continue to follow the Part Schedule of Assessments.

1. Day 0 and Day 1 may be combined on the same day. Additionally, the Day 0 visit may be performed over multiple visits if preformed within the 28-day screening window.
2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for “stay at home” or “shelter in place”), a safety telephone call to the participant should be made in place of the study site visit. The safety telephone call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Home visits will be permitted for all nondosing visits,

with the exception of Screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Home visits must be permitted by the study site IRB and the participant via informed consent/assent and have prior approval from the Sponsor (or its designee).

3. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 +7 days as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the visit window may be extended to Day 29 + 21 days. When the extended visit window is used, the remaining study visits should be rescheduled to follow the inter-visit interval from the actual date of the second dose.
4. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363.
5. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.
6. The Participant Decision visit may be performed over multiple visits. Once the Participant Decision Visit has been initiated, all assessments must be completed within a 7-day period.
7. Physical examination: A full physical examination, including height and weight, will be performed at Day 1, Day 29, Day 57, Day 209, and Day 394. BMI will be calculated only at Screening Visit (Day 0). Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE. Vital signs are to be measured pre- and post dose on days of injection (Day 1 and Day 29). When applicable, vital signs should be measured before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on Day 1 or Day 29 must have the visit rescheduled within the relevant visit window to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
8. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time.
9. Sample must be collected prior to dosing of injection on Day 1.
10. The nasopharyngeal swab sample will be used to ascertain the presence of SARS-CoV-2 via RT-PCR.
11. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for Covid-19, or new or ongoing AEs. If a participant meets the prespecified criteria of suspicion for COVID-19 (Section 7.1.6), the participants will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit, to include an NP swab sample (for RT-PCR testing) and other clinical evaluations. If a study site visit is not possible, a home visit may be arranged to collect the NP sample and conduct clinical evaluations. If a home visit is not possible, the participant will be asked to submit a saliva sample to the study site by a Sponsor-approved method. At this illness visit, the NP swab samples will be collected to evaluate for the presence of SARS-CoV-2 infection. NP swab samples will also be tested for the presence of other respiratory pathogens. In addition, the study site may collect an additional NP sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
12. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection
13. Diary entries will be recorded by the participant at approximately 30 minutes after injection while at the study site with instruction provided by study staff. Study participants will continue to record entries in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolves or the next IP injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via telephone call or at the following study visit.
14. Trained study site personnel will call all participants to collect information relating to any AEs, MAAEs, SAEs, AEs leading to study withdrawal, information on concomitant medications associated with those events, and any nonstudy vaccinations. In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms.
15. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).

Table 8: Participant Decision Clinic Visit

	All Participants
Return to clinic for Participant Decision Clinic Visit	X
Sign revised Informed Consent Form	X
Confirm participant's choice to be unblinded or not to be unblinded	X
Confirm participant's choice to receive open-label mRNA-1273	X
Nasopharyngeal swab	X
Blood for immunologic analysis	X
Counsel about public health measures to limit virus spread[1]	X

1. All participants are counseled about the importance of continuing other public health measures to limit the spread of disease including physical-social distancing, wearing a mask, and hand-washing.

Figure 4: Schedule of Part A and Part B Participant Visits During the Part B Open-label Period

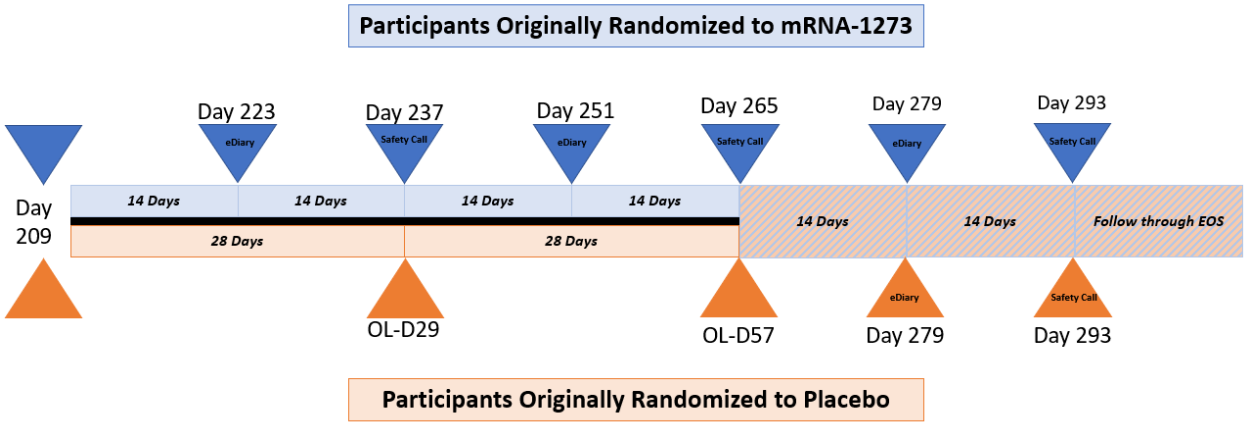


Table 9: Schedule of Assessments Part B, Open-label Observational Phase for Participants Who Previously Received Placebo

Visit Number	7	8	9
Type of Visit	C	C	C
Study Visit Day	(D209/ Decision Visit) OL-D1	OL-D29	OL-D57[1]
Window Allowance (Days)	+7	-3/+7	±14
Days Since Most Recent Injection	0	28	28
Informed consent form	These assessments are already performed as part of the regular D209 visit.		
Blood for vaccine immunogenicity			X
Nasopharyngeal swab sample for SARS-CoV-2[2]		X	X
Physical examination including vital signs[3]	PE including vitals performed as part of D209 visit.	X	X
	X Vitals obtained post dose.	X	
Pregnancy testing	X	X	
Study injection (including 30-minute post-dosing observation period)	X	X	
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[5]	X	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[4]	X	X	X
Recording of AESI (MIS-C)	X	X	X
Recording of concomitant medications and non-study vaccinations[4]	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; C = clinic visit; M = month; MAAE = medically attended AE; MIS-C = multisystem inflammatory syndrome of children; SC = safety (telephone) call; SFU = Safety Follow Up; SAE = serious adverse event.

1. After the OL-D57 visit, Part B participants will revert to the Part A SoA, re-entering at Day 265 as shown in Figure 4.
2. The nasopharyngeal swab sample, collected prior to vaccination on days of injection, will be used to ascertain the presence of SARS-CoV-2 via PCR.
3. Physical examination: A symptom-directed physical examination will be performed at OL-Day 1, OL-Day 29, and OL-D57. Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. Any clinically significant finding identified during a study visit should be reported as an MAAE. Vital signs are to be collected pre- and post-dosing on days of injection (OL-Day 1 and OL-Day 29). When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on OL-Day 1 or OL-Day 29 must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be administered investigational product at the discretion of the investigator
4. All concomitant medications and non-study vaccinations will be recorded through 28 days post-injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (OL-Day 57).

10.2. APPENDIX 2: Study Governance Considerations

10.2.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.2.2. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor or its representatives will visit the investigational study site to do the following:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a clinical study agreement between the Sponsor, the designated CRO, and the investigator.

According to ICH GCP guidelines, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the Clinical Monitoring Plan. During the study, a monitor from the Sponsor or a representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the SAE Hotline, and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

10.2.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct study site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow the Sponsor, their designee(s), the IRB, or regulatory

authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and any IRB may visit the study site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH E6(R2) GCP, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The principal investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the participant consent/assent form and recruitment materials, must be maintained by the investigator and made available for inspection.

10.2.4. Financial Disclosure

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

The Sponsor, the CRO, and the study site are not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor, the CRO, and the study site are not financially responsible for further treatment of the disease under study.

10.2.5. Recruitment Procedures

Advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant should be submitted to the Sponsor for approval. All documents must be approved by the IRB.

10.2.6. Informed Consent/Assent Process

The informed consent/assent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act, where applicable, and the IRB or study site. All consent documents will be approved by the appropriate IRB. The actual ICF used at each study site may differ, depending on local regulations and IRB requirements. However, all versions of the ICF must contain the standard information found in the

sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IRB prior to the ICF being used.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to them in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

The investigator is responsible for ensuring that the participant fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible.

No participant should be obliged to participate in the study. The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) LARs must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

The participant must be allowed sufficient time to decide whether they wish to participate in the study.

The participant must be made aware of, and give consent to, direct access to his/her source medical records by study monitors, auditors, the IRB, and regulatory authorities. The participant should be informed that such access will not violate participant confidentiality or any applicable regulations. The participant and/or participants' parent(s)/LAR(s) should also be informed that he/she is authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participant and/or participants' parent(s)/LAR(s).

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date (within the initial Screening Period).

The ICF will also explain that excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoVs.

10.2.7. Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and the Sponsor.

IRB approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such an amendment will be released by the Sponsor, agreed by the investigator(s), and approved by the relevant IRB(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents, and the ICF have been approved by relevant IRB(s) must to be provided to the Sponsor before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed by the investigators, and notified to the IRB(s).

10.2.8. Protocol Deviations

The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of protocol deviations, corrective actions are to be developed by the study site and implemented promptly.

After a participant proceeds to the Participant Decision Visit (Part A) of the study, participants who received mRNA-1273 will continue to follow the open-label Part A SoA. Participants who received placebo will transition to open-label Part B of the study and will follow the Part B SoA (Table 9) through OL-Day 57. At this point, Part B participants will return to the Part A SoA (Table 7) until study completion.

It is the responsibility of the study site investigator to use continuous vigilance to identify and report protocol deviations to the Sponsor or its designee. All protocol deviations must be addressed in study source documents, reported to study monitor. Protocol deviations must be sent to the reviewing IRB per their policies. The study site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.2.9. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by clinical quality assurance (QA) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being. Each participant will be asked to complete a form allowing the investigator to notify the participant's primary health care provider of his/her participation in this study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

10.2.10. Sample Retention and Future Biomedical Research

The retention period of laboratory samples will be 20 years, or as permitted by local regulations, to address further scientific questions related to mRNA-1273 or antirespiratory virus immune response. In addition, identifiable samples can be destroyed at any time at the request of the participant. During the study, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other Ab-based methodologies on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1273, as well as to determine how changes in biomarkers may relate to exposure and clinical outcomes. A decision to perform such exploratory research may arise from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

10.2.11. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publically accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), as well as some national registries.

In addition, results from clinical trials are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available, the privacy of participants in clinical studies sponsored by the Sponsor is assured. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.2.12. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the study site under the supervision of the study site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CRO).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A QA representative from the Sponsor or a qualified designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

10.2.13. Data Collection and Management

This study will be conducted in compliance with ICH CGP guidelines. This study will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This study will use electronic data collection to collect data directly from the study site using eCRFs. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using WHO - Drug Dictionary.

10.2.14. Source Documents

Source documents are original documents or certified copies, and include, but are not limited to, eDiaries, medical and hospital records, screening logs, informed consent/assent forms, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's study site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Sponsor or its designee requires that the investigator prepare and maintain adequate and accurate records for each participant treated with the IP. Source documents such as any hospital, clinic, or office charts, and the signed ICFs are to be included in the investigator's files with the participant's study records.

10.2.15. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is > 2 years.

If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

10.2.16. Study and Site Closure

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Continuation of the study represents a significant medical risk to participants
- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further mRNA-1273 development

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

10.2.17. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

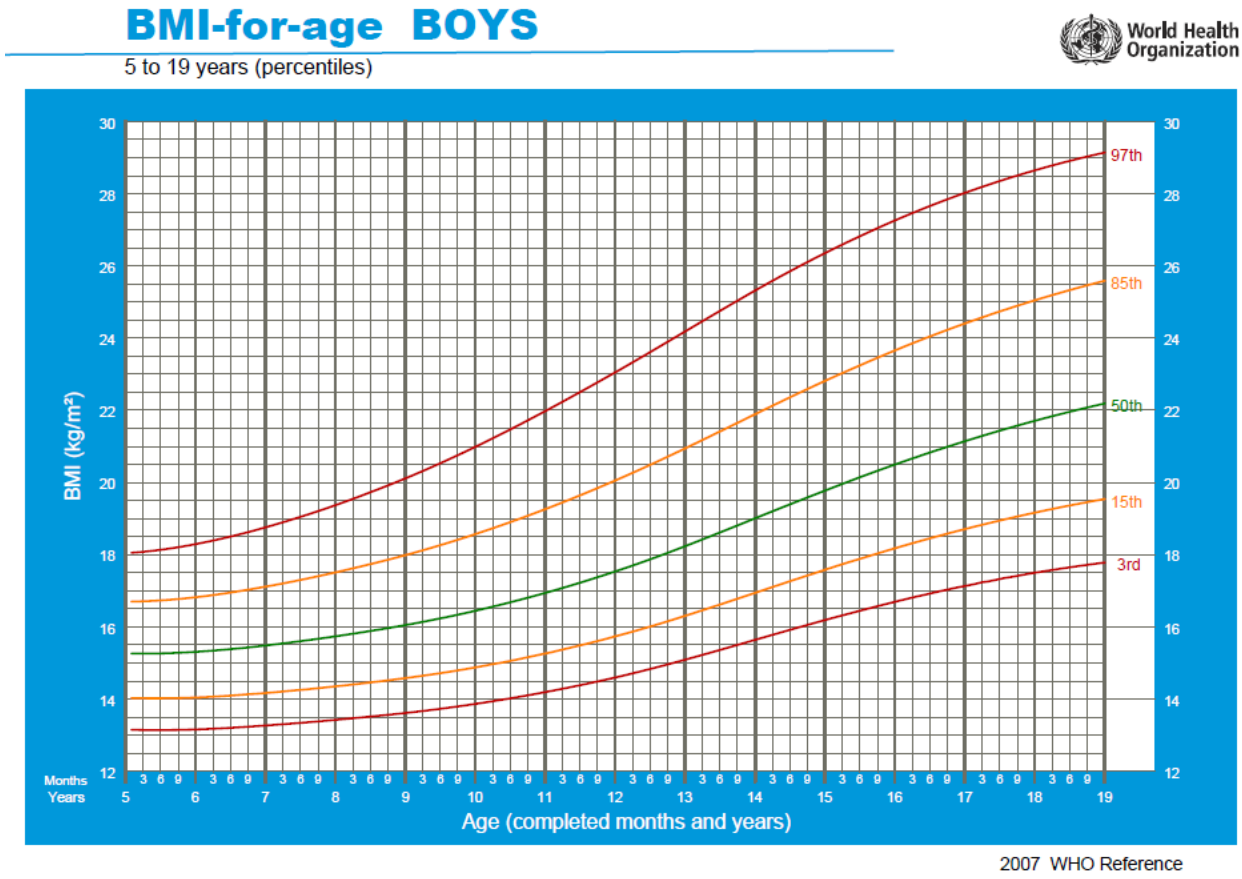
The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

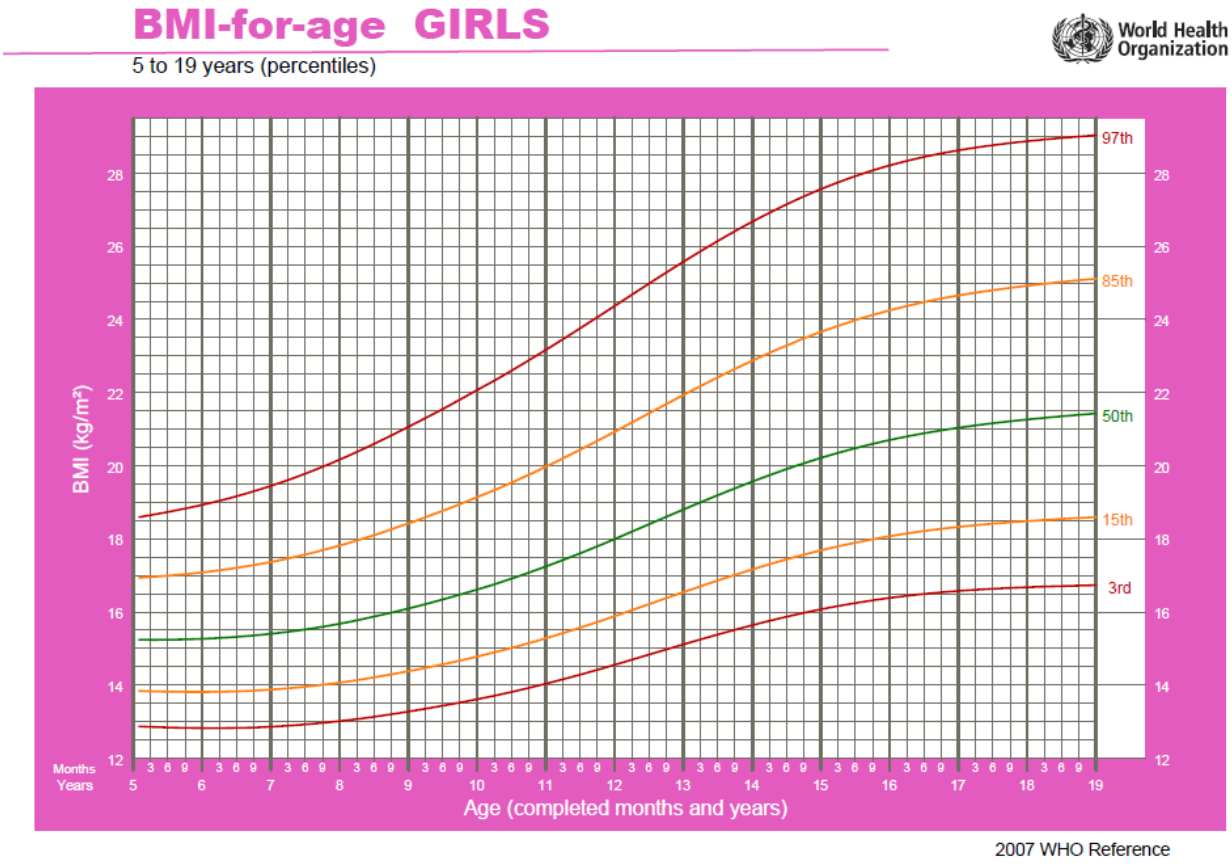
The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

10.2.18. Body Mass Index (BMI) Charts for Boys and Girls

For boys aged 5 through 19 years:



For girls aged 5 through 19 years:



10.3. APPENDIX 3: Contraceptive Guidance

Woman of Childbearing Potential (WOCBP)

Females of childbearing potential are those who are considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below). If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal, surgically sterile female with 1 of the following:
    a. Documented complete hysterectomy
    b. Documented surgical sterilization

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study entry.

    Note: Documentation can come from the study site personnel's review of the participant's medical records, medical examination, or medical history interview.

Contraception Guidance:

Adequate female contraception is defined as consistent and correct use of an FDA-approved contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device
- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note that periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

Signature Page for VV-CLIN-002163 v1.0

Approval	Roderick McPhee Medical 30-Mar-2021 16:27:50 GMT+0000

Signature Page for VV-CLIN-002163 v1.0

CLINICAL STUDY PROTOCOL

Protocol Title:	A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age
Protocol Number:	mRNA-1273-P203
Sponsor Name:	ModernaTX, Inc.
Legal Registered Address:	200 Technology Square Cambridge, MA 02139
Sponsor Contact and Medical Monitor:	Roderick McPhee, MD, PhD ModernaTX, Inc. 200 Technology Square Cambridge, MA 02139 Telephone: 1-617-301-1186 e-mail: Roderick.McPhee@modernatx.com
Regulatory Agency Identifier Number(s):	IND: 019745
Approval Date:	04 Nov 2020

CONFIDENTIAL

All financial and nonfinancial support for this study will be provided by ModernaTX, Inc. The concepts and information contained in this document or generated during the study are considered proprietary and may not be disclosed in whole or in part without the expressed written consent of ModernaTX, Inc. The study will be conducted according to the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance.*

PROTOCOL APPROVAL – SPONSOR SIGNATORIES

Study Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age

Protocol Number: mRNA-1273-P203

Protocol Date: 04 Nov 2020

Protocol accepted and approved by:

See esignature and date signed on last page of document.

Roderick McPhee, MD
Clinical Development, Infectious Disease
ModernaTX, Inc
200 Technology Square
Cambridge, MA 02139
Telephone: 1-617-682-2724

Date

DECLARATION OF INVESTIGATOR

I have read and understood all sections of the protocol entitled "A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age" and the most recent version of the investigator's brochure.

I agree to supervise all aspects of the protocol and to conduct the clinical investigation in accordance with the current Protocol, the *International Council for Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use, E6(R2) Good Clinical Practice (GCP) Guidance*, and all applicable government regulations. I will not make changes to the protocol before consulting with ModernaTX, Inc. or implement protocol changes without Institutional Review Board (IRB) approval except to eliminate an immediate risk to participants.

I agree to administer study treatment only to participants under my personal supervision or the supervision of a sub-investigator. I will not supply study treatment to any person not authorized to receive it. I also agree that persons debarred from conducting or working on clinical studies by any court or regulatory agency will not be allowed to conduct or work on studies for the sponsor or a partnership in which the sponsor is involved. I will immediately disclose it in writing to the sponsor if any person who is involved in the study is debarred, or if any proceeding for debarment is pending, or, to the best of my knowledge, threatened.

I will not disclose confidential information contained in this document including participant information, to anyone other than the recipient study staffs and members of the IRB. I agree to ensure that this information will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent from ModernaTX, Inc. I will not disclose information regarding this clinical investigation or publish results of the investigation without authorization from ModernaTX, Inc.

The signature below provides the necessary assurance that this study will be conducted according to all stipulations of the protocol, including statements regarding confidentiality, and according to local legal and regulatory requirements, US federal regulations, and ICH E6(R2) GCP guidelines.

Signature of principal investigator	Date
Printed name of principal investigator	

PROTOCOL SYNOPSIS

Name of Sponsor/Company: ModernaTX, Inc.

Name of Investigational Product: mRNA-1273 for injection

Name of Active Ingredient: mRNA-1273

Protocol Title: A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 years of age

Protocol Number: mRNA-1273-P203

Study Period (years): Approximately 1 year

Phase of Development: Phase 2/3

Estimated date first participant enrolled: 30 Nov 2020

Estimated date last participant completed: 30 Jun 2022

Total Number of Sites: Approximately 15 to 25 study sites in the United States or its territories.

Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of 100 μg of mRNA-1273 vaccine administered in 2 doses 28 days apart	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs through the entire study period • AESI of MIS-C through the entire study period • Vital sign measurements

	• Physical examination findings
• To infer efficacy of mRNA-1273 (100 µg, 2 doses 28 days apart), serum Ab responses obtained 28 days after the second injection of mRNA-1273 (Day 57) will be either: – Evaluated against an accepted Ab threshold of protection against COVID-19 (if established in Study P301) – Compared to GM values of serum Ab obtained from adult recipients of mRNA-1273 in the clinical endpoint efficacy trial (Study P301)	• The proportion of participants with a serum Ab level at Day 57 ≥ an Ab threshold of protection[1] • The GM value of serum nAb level from Study P203 vaccine recipients at Day 57 compared with GM value of serum nAb level obtained from adult vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301)[2] 1. If an accepted serum nAb threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy 2. If a threshold is not available, efficacy will be inferred based on establishing noninferiority of adolescent (12 to < 18 years; this clinical study) to adult GM values of serum nAb obtained in Study P301 (GM value 12 to < 18 years / GM value ≥ 18 years).
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of SARS-CoV-2 S2P-specific bAb through 1 year after dose 2	• The GM value of SARS-CoV-2 S2P-specific bAb on Day 1, Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2)
• To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of nAb through 1 year after dose 2	• The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2)
• To evaluate the effect of mRNA-1273 on the incidence of SARS-CoV-2 infection compared with the incidence among placebo recipients	• The incidence of SARS-CoV-2 infection starting on Day 57 among recipients of mRNA-1273 and placebo will be compared

	• SARS-CoV-2 infection will be defined by detection of Ab against a nonvaccine antigen (eg, nucleocapsid protein); the definition of infection is dependent on baseline serostatus: – Participants seronegative at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein either from below the LOD or LLOQ at Day 1 that increase to above or equal to LOD or LLOQ starting at Day 57 or later. – Participants seropositive at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein above the LOD or LLOQ at Day 1 that increase by 4-fold or more in participants with pre-existing bAb starting at Day 57 or later.
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with SARS-CoV-2 infection AND positive RT-PCR for SARS-CoV-2	• Vaccine efficacy of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 is defined as symptomatic disease based on the following criteria: – The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥ 100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR – The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND – The participant must have at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if

	hospitalized) positive for SARS-CoV-2 by RT-PCR
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence
• To describe the ratio or profile of specific bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; COVID-19 = coronavirus disease 2019; GM = geometric mean; IP = investigational product; LLOQ = lower limit of quantification; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; nAb = neutralizing antibody; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; S2P = S protein; SAE = severe adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

Overall Study Design

This is a Phase 2/3, randomized, observer-blind, placebo controlled study to evaluate the safety, reactogenicity, and effectiveness of mRNA-1273 Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) vaccine in healthy adolescents 12 to < 18 years of age.

Participants will be randomly assigned to receive injections of either 100 µg of mRNA-1273 vaccine or a placebo control in a 2:1 randomization ratio.

The goal of the study is to seek an indication for use of mRNA-1273 (100 µg intramuscular [IM], given as 2 injections, 28 days apart) in the 12 to < 18 years age group. The basis for demonstrating vaccine effectiveness is proposed to be met by serum antibody (Ab) response measured in this adolescent age group. The approach to inferring vaccine effectiveness will depend on whether an accepted serum Ab threshold conferring protection against coronavirus disease 2019 (COVID-19) has been established. If an Ab threshold of protection has been established, effectiveness will be inferred based on the proportion of adolescent study participants with serum Ab levels (on Day 57) that meet or exceed the Ab threshold. If an Ab threshold of protection has not been established, effectiveness will be inferred based on demonstrating noninferiority of the geometric mean (GM) value of serum neutralizing antibody

(nAb) from adolescent participants compared with the GM value of serum nAb from adults enrolled in the ongoing clinical endpoint efficacy trial (Study P301).

This study in adolescents will monitor all participants for a total of 12 months following the second dose of vaccine or placebo. Safety assessments will include solicited adverse reactions (ARs; 7 days after each injection), unsolicited adverse events (AEs; 28 days after each injection), medically attended adverse events (MAAEs), serious adverse events (SAEs), and adverse events of special interest (AESIs) (multisystem inflammatory syndrome in children [MIS-C]) throughout the study period.

Blood samples will be collected from all participants at baseline (Day 1), Day 57 (28 days after dose 2), Day 209 (6 months after dose 2), and Day 394 for measurement of SARS-CoV-2 specific binding and nAb responses. Blood samples will also be tested for the development of Ab directed against nonvaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2.

The incidence of SARS-CoV-2 infection among vaccine recipients and placebo recipients will be compared to assess the potential for mRNA-1273 to reduce the rate of infection in vaccine recipients.

This study comprises 8 scheduled visits including a screening visit and 7 scheduled visits, of which Visit 2 and Visit 4 will be virtual/telephone visits and the other visits will be in-clinic visits. This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements.

Safety Oversight:

Safety oversight will be under the direction of a Data Safety Monitoring Board composed of external independent consultants with relevant expertise.

The contract research organization's medical monitor, the Sponsor's medical monitor, and the individual study site investigators will monitor safety throughout the study.

Study Duration: The study duration will be approximately 14 months, which includes 1 month for screening (Day -28 to Day 1), 1 month for dosing (on Day 1 and Day 29), and 12 months of follow-up after the second dose to monitor for safety, immunogenicity, and efficacy.

Number of Participants: Approximately 3,000 participants will be enrolled.

Study Eligibility Criteria:

Inclusion Criteria:

Each participant must meet all of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, 12 to < 18 years of age at the time of consent (Screening Visit, Day 0) who, in the opinion of the investigator, is in good general health based on review of medical history and screening physical examination.
2. Investigator assessment that the participant, in the case of an emancipated minor, or parent(s)/legally acceptable representative(s) [LAR(s)] understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures and provides written informed consent/assent.
3. Body mass index (BMI) at or above the third percentile according to World Health Organization (WHO) Child Growth Standards at the Screening Visit (Day 0).
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche or surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy).
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test at Screening (Day 0), on the day of the first injection (Day 1), and on the day of the second injection (Day 29)
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1)
    - Has agreed to continue adequate contraception through 3 months following the second injection (Day 29)
    - Is not currently breastfeeding.

Exclusion Criteria:

Participants who meet any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known history of SARS-CoV-2 infection or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to vaccine administration.

2. Travel outside of the United States in the 28 days prior to the Screening Visit (Day 0).
3. Pregnant or breastfeeding.
4. Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
5. Prior administration of an investigational CoV (eg, Severe Acute Respiratory Syndrome coronavirus 2 [SARS-CoV-2], Severe Acute Respiratory Syndrome coronavirus [SARS-CoV], Middle East Respiratory Syndrome coronavirus [MERS-CoV]) vaccine.
6. Current treatment with investigational agents for prophylaxis against COVID-19.
7. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
8. Current use of any inhaled substance (eg, tobacco or cannabis smoke, nicotine vapors).
9. History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).
10. History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of screening.
11. History of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
    - Congenital or acquired immunodeficiency, including human immunodeficiency virus (HIV) infection
    - Suspected active hepatitis
    - Has a bleeding disorder that is considered a contraindication to IM injection or phlebotomy
    - Dermatologic conditions that could affect local solicited AR assessments
    - History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine
    - Diagnosis of malignancy within the previous 10 years (excluding nonmelanoma skin cancer)
    - Febrile seizures

12. Receipt of:
    - Any licensed vaccine within 28 days before the first dose of IP or plans for receipt of any licensed vaccine through 28 days following the last dose of IP.
    - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 20 mg/day prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the day of enrollment. Participants may have visits rescheduled for enrollment if they no longer meet this criterion within the Screening Visit window. Inhaled, nasal, and topical steroids are allowed.
    - Intravenous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrollment.
13. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.
14. Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.
15. Is an immediate family member or has a household contact who is an employee of the research center or otherwise involved with the conduct of the study.

Study Treatment:

Investigational Product:

The investigational product (mRNA-1273 vaccine) is a lipid nanoparticle (LNP) dispersion of a messenger RNA (mRNA) encoding the prefusion stabilized spike (S) protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (PEG2000-DMG). mRNA-1273 injection is provided as a sterile liquid for injection, white to off-white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

Mode of Administration:

Doses will be administered by IM injection into the deltoid muscle according to the procedures specified in the mRNA-1273-P203 Pharmacy Manual. Preferably, both doses should be administered into the nondominant arm.

Procedures and Assessments:

Safety Assessments:

Safety assessments will include monitoring and recording of the following for each participant:

- Solicited local and systemic ARs that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using electronic diaries (eDiaries).
- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days)
- AEs leading to discontinuation from dosing and/or withdrawal from study participation from Day 1 through the last day of study participation
- MAAEs from first dose on Day 1 through the entire study period
- SAEs from first dose on Day 1 through the entire study period
- AESI of MIS-C through the entire study period
- Vital sign measurements
- Physical examination findings
- Assessments for SARS-CoV-2 infection from Day 1 through study completion
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study

Immunogenicity Assessments:

The following analytes will be measured in blood samples for immunogenicity assessments:

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays
- Serum binding antibody (bAb) against SARS-CoV-2 nucleocapsid protein measured by ligand-binding assay specific to the SARS-CoV-2 S protein
- Qualitative and quantitative measure of viral load against SARS-CoV-2 as measured by reverse transcriptase polymerase chain reaction (RT-PCR)

Efficacy Assessments:

Vaccine effectiveness for adolescents of ages of 12 to < 18 years will be inferred based on serum Ab responses obtained on Day 57 (28 days after the second injection of mRNA-1273). Inference will be based on assessing the adolescent Ab responses against the following:

1. *If available at the time of analysis*, adolescent Ab responses will be assessed against an accepted serum Ab threshold conferring protection against COVID-19.
2. *If an accepted threshold of protection is not available*, adolescent Ab responses will be assessed by establishing noninferiority of the GM value of serum nAb from adolescent participants compared with the GM value of serum nAb from adults enrolled in the ongoing clinical endpoint efficacy trial (Study P301).

Statistical Methods:

Hypothesis Testing:

If an accepted threshold based on SARS-CoV-2 S protein (S2P) is established for the primary immunogenicity objective, the null hypothesis is that the percentage of participants on mRNA-1273 with SARS-CoV-2 S2P serum Ab above the established threshold on Day 57 is ≤ 60% (ie, H_0: percentage of participants on mRNA-1273 ≤ 60% with SARS-CoV-2 S2P serum Ab on Day 57 above the established threshold).

The study would be considered to meet the immunogenicity objective if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 60% (lower bound of the 95% CI > 60%).

If an accepted serum Ab threshold of protection against COVID-19 is not available for the primary immunogenicity objective, the null hypothesis will be based on SARS-CoV-2 S2P nAb.

H_0: immunogenicity response to mRNA-1273 is inferior in adolescents (12 to < 18 years of age) compared with that in adults (≥ 18 years of age) using mRNA-1273 Study P301 data, based on SARS-CoV-2 S2P serum nAb on Day 57.

The study would be considered to meet the primary immunogenicity objective if noninferiority in immune response in adolescents compared with that in adults is demonstrated by the lower bound of the 95% CI of the geometric mean ratio (GMR) rules out 0.5 (lower bound > 0.5) using a noninferiority margin of 2. The GMR is the ratio of the GM value of adolescents on mRNA-1273 in this Study P203 compared with the GM value of adults on mRNA-1273 in Study P301 on Day 57.

Power and Sample Size:

The sample size of this study is driven by safety. Approximately 3,000 participants will be randomly assigned in a 2:1 ratio to receive mRNA-1273 or placebo. With 2,000 participants

exposed to mRNA-1273, the study has at least 90% probability to observe at least 1 participant with an AE at a true 0.25% AE rate.

Serum samples from all participants will be collected and banked, a subset of participants will be selected, and their samples will be processed for immunogenicity testing (the Immunogenicity Subset).

Approximately 210 participants who receive mRNA-1273 will be selected for the Immunogenicity Subset, with a target of 178 participants in the Per-Protocol (PP) Immunogenicity Subset (adjusting for approximately 15% of participants who may be excluded from the PP Immunogenicity Subset, as they may not have immunogenicity results due to any reason). The sample size of the Immunogenicity Subset may be updated with data from other mRNA-1273 studies or external data especially regarding a threshold of protection. In such a situation, the final sample size of the Immunogenicity Subset will be documented in the statistical analysis plan (SAP).

For the primary immunogenicity objective, with approximately 178 participants, the study will have > 90% power to rule out 60% with a 2-sided 95% CI for the percentage of mRNA-1273 participants exceeding the acceptable threshold if the true rate of participants exceeding the acceptable threshold is 75%. With approximately 178 participants, there will be 90% power to demonstrate noninferiority of the immune response in adolescents at a 2-sided alpha of 0.05, compared with that in adults (in Study P301) receiving mRNA-1273, assuming an underlying GMR value of 1 and a noninferiority margin of 2. The standard deviation of the log-transformed levels is assumed to be 2.

Analysis Sets:

The analysis sets are defined in the following table:

Analysis Set	**Description**
Randomization Set	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received at least 1 injection of IP.
Analysis Set	**Description**
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing.
Per-protocol (PP) Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset who

	received planned doses of study vaccination per schedule, complied with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. Participants who are seropositive at baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for analyses of immunogenicity unless specified otherwise.
PP Set for Efficacy	All participants in the FAS who received planned doses of study vaccination, had no immunologic or virologic evidence of prior COVID-19, and have no major protocol deviations that impact key or critical efficacy data.
Solicited Safety Set	The Solicited Safety Set consists of FAS participants who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Safety Set	All randomized participants who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for the solicited ARs.

Abbreviations: AR = adverse reaction; COVID 19 = coronavirus disease 2019; IP = investigational product.

Safety Analyses:

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by treatment group.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to withdrawal, vital sign measurements, and physical examination findings. The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be summarized.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each dose will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from IP or withdrawal from the study

will be summarized. Unsolicited AEs will be presented by the Medical Dictionary for Regulatory Activities (MedDRA) preferred term and system organ class.

The number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summary tables accordingly.

Immunogenicity Analyses:

The SAP will describe the complete set of immunogenicity analyses, including the approach to sample participants into an Immunogenicity Subset for analysis of immunogenicity. The PP Immunogenicity Subset is the primary analysis set for immunogenicity unless otherwise specified. The primary immunogenicity objective of this study is to use the immunogenicity response to infer efficacy in adolescents (12 to < 18 years in this study).

If an accepted serum Ab threshold of protection against COVID-19 is available based on data from other mRNA-1273 studies or external data, the number and percentage of participants with Ab greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. If the lower bound of the 95% CI on the mRNA-1273 group is > 60%, the primary immunogenicity objective of this study will be considered to be met.

The percentage of participants with serum Ab greater than or equal to the threshold with 95% CI will be provided by vaccination group (mRNA-1273 and placebo) at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

The GM level of serum Ab with corresponding 95% CI will be provided at each time point by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

In addition, an analysis of covariance (ANCOVA) model with vaccination group as explanatory variables, adjusting for baseline value if applicable, will be used to assess the effect of mRNA-1273 at postbaseline time points with Day 57 as the time point of primary interest. The geometric least squares mean (GLSM) with 95% CI for each vaccination group and GMR with 95% CI for difference between mRNA-1273 and placebo will be estimated from the ANCOVA model. If an accepted serum Ab threshold of protection against COVID-19 is not established, the non-inferiority of immune response in adolescents compared with that in adults will be assessed. Noninferiority of the immune response in adolescents in this study at a 2-sided alpha of 0.05, compared with that in adults in Study P301 receiving mRNA-1273, will be considered to be demonstrated if the lower bound of the 95% CI of GMR is > 0.5 using a noninferiority margin of 2.

For SARS-CoV-2 S2P-specific bAb, the number and percentage of participants with seroconversion due to vaccination, GM level for specific nAb and bAb, GMFR of nAb and bAb

with corresponding 95% CI will be provided at each time point with Day 57 as the primary time points of interest.

Efficacy Analyses:

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate will be provided by vaccination group, calculated as the number of cases divided by the total person-time. The incidence rate ratio of mRNA-1273 versus placebo will be provided with 95% CI computed using the exact method conditional upon the total number of cases adjusted by the total person-time.

For serologically-confirmed SARS-CoV-2 infection or COVID-19, regardless of symptomatology or severity, infection rate will be provided by vaccination group and the infection rate ratio of mRNA-1273 versus placebo with its 95% CI using the exact method conditional upon the total number of cases adjusted by the total person-time.

Study Analyses:

Interim Analyses:

An interim analysis of safety and immunogenicity data is planned following Day 57 (1 month after dose 2). At the Sponsor's discretion, a CSR may be developed for the interim analysis.

Final Analysis:

The final analysis of all endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in a final CSR, including individual listings.

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LIST OF ABBREVIATIONS AND TERMS

The following abbreviations and terms are used in this study protocol.

Abbreviation or Specialist Term	Definition
Ab	antibody
AE	adverse event
AESI	adverse event of special interest
ANCOVA	analysis of covariance
AR	adverse reaction
ARDS	Acute Respiratory Distress Syndrome
bAb	binding antibody
BMI	body mass index
CBER	Center for Biologics and Evaluation Research
CD	cluster of differentiation
CDC	US Centers for Disease Control and Prevention
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	clinical laboratory improvement amendments
CONSORT	Consolidated Standards of Reporting Trials
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CRO	contract research organization
CSR	clinical study report
DMID	Division of Microbiology and Infectious Diseases
DSMB	Data Safety Monitoring Board
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form

Abbreviation or Specialist Term	Definition
EDC	electronic data capture
eDiary	electronic diary
EOS	end of study
ERD	enhanced respiratory disease
ESR	erythrocyte sedimentation rate
FAS	full analysis set
FDA	US Food and Drug Administration
FIO2	fraction of inspired oxygen
GCP	Good Clinical Practice
GLSM	geometric least squares mean
GM	geometric mean
GMR	geometric mean ratio
HCP	healthcare practitioner
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
ICU	intensive care unit
IL-6	interleukin 6
IM	intramuscular(ly)
IND	investigational new drug
IP	investigational product
IRB	institutional review board
IRT	interactive response technology
LAR	legally acceptable representative
LDH	lactic acid dehydrogenase
LLOQ	lower limit of quantification

Abbreviation or Specialist Term	Definition
LNP	lipid nanoparticle
LOD	limit of detection
LTFU	lost to follow-up
MAAE	medically attended adverse event
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
MIS-C	multisystem inflammatory syndrome in children
mRNA	messenger RNA
nAb	neutralizing antibody(ies)
NHP	nonhuman primate
NIAID	National Institute of Allergy and Infectious Diseases
NP	nasopharyngeal
Study P301	Study mRNA-1273-P301; NCT04470427
PaO2	partial pressure of oxygen
PCR	polymerase chain reaction
PEG2000-DMG	1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000
PP	per protocol
QA	quality assurance
RT-PCR	reverse transcriptase polymerase chain reaction
S	spike
S2P	S protein
SAE	serious adverse event
SAP	statistical analysis plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe Acute Respiratory Syndrome coronavirus 2
SD	standard deviation

Abbreviation or Specialist Term	Definition
SM-102	eptadecane-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate
SoA	schedule of assessments
SpO2	oxygen saturation
SUSAR	suspected unexpected serious adverse reaction
Th1	T helper cell 1
WHO	World Health Organization
WOCBP	woman of childbearing potential

1. INTRODUCTION

1.1. Study Rationale

Coronaviruses (CoVs) are a large family of viruses that cause illness ranging from the common cold to more severe diseases, such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). Coronaviruses are zoonotic, meaning they are transmitted between animals and people. An outbreak of the CoV disease 2019 (COVID-19) caused by Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, Hubei Province, China in December 2019 and has spread throughout China and to over 215 other countries, territories, and areas including the United States (WHO 2020a). On 11 Mar 2020, the World Health Organization (WHO) officially declared COVID-19 a pandemic. As of 28 Sep 2020, the WHO dashboard (WHO 2020b) reported there have been nearly 1 million COVID-19 deaths worldwide and more than 200,000 deaths in the United States.

As of 21 Sep 2020, the US Centers for Disease Control and Prevention (CDC) reported over 6.7 million confirmed and probable cases of COVID-19 in all 50 states and 5 jurisdictions, with over 199,000 attributed and probable deaths (CDC 2020a). While the CDC have reported that the highest risk of disease burden is in older adults and populations with certain underlying comorbid conditions such as heart disease, diabetes, and lung disease, the burden in the pediatric population is not negligible. Rather, evidence is emerging (described below) to suggest that children < 18 years of age, particularly adolescents, may be disproportionately contributing to the number of new cases as schools re-open for varying degrees of in-person learning. As of 21 Sep 2020, the CDC reported over 408,000 cases of COVID-19 in children less than 18 years of age (8.1% of all US cases) and 88 deaths (< 0.1% of all US deaths; CDC 2020b).

During the incubation period, those infected can also transmit the virus (Chen et al 2020). Person-to-person transmission occurs primarily via direct contact or through droplets spread by coughing or sneezing from an infected individual, whether symptomatic or not (Rothan and Byrareddy 2020; Chen et al 2020; Licciardi et al 2020; Shen et al 2020). SARS-CoV-2 can also be transmitted via the fecal-oral pathway (Cruz and Zeichner 2020).

During this COVID-19 pandemic, children throughout much of the world have had school attendance limited in an attempt to control infection. Therefore, the main source of infection for SARS-CoV-2 in children, with or without clinical symptoms, is infected household contacts. Indeed, a retrospective cohort study of high school students, parents and siblings of students, and school staff conducted in France in early April 2020 suggests that there was little to no transmission from infected students to other students or school staff. Rather, a high prevalence of antibodies against SARS-CoV-2 among families suggests familial clustering of COVID-19 cases (Fontanet et al 2020).

A recent report of COVID-19 trends in school-aged children in the United States from 01 Mar 2020 to 19 Sep 2020 indicates that 37% of laboratory-confirmed cases of COVID-19 in school-aged children occurred in children 5 to 11 years of age while 63% occurred in adolescents 12 to 17 years of age (Leeb et al 2020). During this time period, the average weekly incidence among adolescents was 37.4 cases per 100,000 compared with 19.0 per 100,000 for younger children. Among school-aged children with laboratory-confirmed COVID-19, 58% reported at least one symptom and 5% reported no symptoms; although information on symptoms was missing or unknown for 37%. Overall, in this study, 1.2% of school-aged children with COVID-19 were hospitalized, 0.1% required intensive care unit (ICU) admission and < 0.01% died of COVID-19. Furthermore, at least one underlying condition was reported in 3% of adolescents and 2% of younger children. Chronic lung disease, including asthma, was most commonly reported (55%), followed by disability (neurologic or neurodevelopmental disorders, intellectual or physical disability, and vision or hearing impairment; 9%), immunosuppressive conditions (7%), diabetes (6%), psychological conditions (6%), cardiovascular disease (5%), and severe obesity (4%) (Leeb et al 2020).

Another study examined the age distribution of COVID-19 in the United States from May to August 2020 based on 3 indicators: COVID-19-like illness-related emergency department visits, positive reverse transcriptase polymerase chain reaction (RT-PCR) results for SARS-CoV-2, and confirmed COVID-19 cases (Boehmer et al 2020). These authors report an estimated mean COVID-19 incidence during this time period of 179.3 cases per 100,000 in individuals 10 to 19 years of age. Generally, the largest increase in incidence during this time period was observed in persons < 30 years of age. Finally, a recent report describes an adolescent (13-year-old female), whose only symptom was nasal congestion, yet who was the index case in an outbreak of COVID-19 across 4 states (Schwartz et al 2020). Infection of this primary individual led to 11 subsequent cases, during July and August 2020, in 5 households all linked to a family gathering suggesting that adolescents can serve as the source of COVID-19 outbreaks within families, even when their symptoms are mild as in this case.

Taken together, the above evidence suggests that the burden of COVID-19 has begun to increase in younger age groups, particularly as schools in the United States have started to reopen for some in-person instruction. Adolescents, who are often mobile and may demonstrate lower compliance with nonpharmaceutical interventions such as mask-wearing and social distancing, also likely represent a segment of the population contributing toward sustained community transmission of SARS-CoV-2 and may spread SARS-CoV-2 within households. A vaccine that prevents COVID-19 and SARS-CoV-2 transmission in adolescents would be a crucial public health tool to help curb the pandemic.

There is currently no vaccine against SARS-CoV-2, and there is an urgent public health need to develop one, there being no proven therapy. ModernaTX, Inc (the Sponsor) has initiated an accelerated development program for mRNA-1273 vaccine against SARS-CoV-2 infection (Section 1.2), most recently initiating a Phase 3 clinical study in the United States involving administration of mRNA-1273 vaccine 100 µg as both an initial dose and a second dose 28 days later (Section 1.2.2).

The objective for this Phase 2/3 study is to evaluate the safety and reactogenicity of a single dose level (100 µg) of mRNA-1273 vaccine administered in 2 doses 28 days apart (Section 3.1) to an adolescent population. Recently, a fractional second dose administered intramuscularly (IM) has been assessed with an adjuvanted malaria vaccine and demonstrated similar immunogenicity with improved efficacy in a controlled human malaria infection model (Regules et al 2016; Moon et al 2020).

1.2. Background and Overview

The Sponsor has developed a rapid-response, proprietary vaccine platform based on a messenger RNA (mRNA) delivery system. The platform is based on the principle and observations that cells in vivo can take up mRNA, translate it, and then display protein viral antigen(s) on the cell surface. The delivered mRNA does not enter the cellular nucleus or interact with the genome, is nonreplicating, and is expressed transiently. Messenger RNA vaccines have been used to induce immune responses against infectious pathogens such as SARS-CoV-2 (NCT04283461, NCT04405076), cytomegalovirus (NCT03382405), metapneumovirus and parainfluenza virus type 3 (NCT03392389), Zika virus (NCT03325075), and influenza virus (NCT03076385 and NCT03345043).

The Sponsor is using its mRNA-based platform to develop a novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine against SARS-CoV-2 (mRNA-1273). mRNA-1273 encodes for the full-length spike (S) protein of SARS-CoV-2. The CoV S protein mediates attachment and entry of the virus into host cells (by fusion), making it a primary target for neutralizing antibodies (nAb) that prevent infection (Johnson et al 2016; Wang et al 2015; Wang et al 2018; Chen et al 2017; Corti et al 2015; Yu et al 2015; Kim et al 2019; Widjaja et al 2019; Corbett et al 2020a; Ju et al 2020; Robbiani et al 2020). It has been confirmed that the stabilized SARS-CoV-2 S2P expresses well and is in the prefusion conformation (Wrapp et al 2020).

The development of the mRNA-1273 vaccine is being accelerated to address the current SARS-CoV-2 outbreak as a result of the uniquely rapid and scalable manufacturing process for mRNA-1273 vaccine.

1.2.1. Nonclinical Studies

Nonclinical studies have demonstrated that CoV S proteins are immunogenic and S protein-based vaccines, including those based on mRNA delivery platforms, are protective in animals. Prior clinical studies of vaccines targeting related CoVs and other viruses have demonstrated that mRNA-based vaccines are safe and immunogenic. mRNA-1273 has shown preliminary evidence of protection against SARS-CoV-2 in studies in young mice (Corbett et al 2020a) and nonhuman primates (NHPs) (Corbett et al 2020b).

In support of the development of mRNA-1273 for prophylaxis against SARS-CoV-2 infection, nonclinical immunogenicity, biodistribution, and safety studies have been completed with similar mRNA-based vaccines formulated in LNPs containing SM-102 (eptadecane-9-yl 8-((2-hydroxyethyl)(6-oxo-6-(undecyloxy)hexyl)amino)octanoate), the novel proprietary lipid used in the mRNA-1273 LNP formulation.

A detailed review of nonclinical experience with mRNA-1273 vaccine is provided in the investigator's brochure (IB).

1.2.2. Clinical Studies

The mRNA-1273 vaccine is currently being evaluated in 3 ongoing trials. The first is a safety and immunogenicity Phase 1 study (NCT04283461) sponsored and conducted by the Division of Microbiology and Infectious Diseases (DMID; investigational new drug application [IND] 019635) of the National Institute of Allergy and Infectious Diseases (NIAID). The Phase 1 study is an open-label, dose-ranging study of mRNA-1273 in healthy adult male and nonpregnant female participants in 3 age groups: age 18 to 55 years, inclusive (60 participants); age 56 to 70 years, inclusive (30 participants); and ≥ 71 years (30 participants). Participants were randomly assigned to 1 of 4 dose levels of mRNA-1273: 25 µg, 50 µg, 100 µg, and 250 µg. Each participant received an identical-dose by IM injection (0.5 mL) of mRNA-1273 on Days 1 and 29 in the deltoid muscle. Monitoring will continue for 12 months after the second injection.

On 14 Jul 2020, a preliminary report of findings in this Phase 1 study through Day 57 for the 18- to 55-year age cohort (25, 100, and 250 µg dosage groups) was published (Jackson et al 2020). Regarding immunogenicity, after the second injection, serum viral neutralizing activity was detected by 2 methods in all 42 participants evaluated (of 45 enrolled), with values generally similar to those in the upper half of the distribution of a panel of control COVID-19 convalescent serum specimens. Regarding safety, no serious adverse events (SAEs) were reported and no study halting rules were triggered. In general, solicited systemic adverse reactions (ARs) were more common after the second injection. Solicited adverse events (AEs) that occurred in more than half the participants included fatigue, chills, headache, myalgia, and pain at the injection site. While no participants at any dosage level (N=45) experienced fever following the first dose, mild fever was

observed in 5 participants (33%), moderate fever in 1 participant (6.7%), and no participants experienced severe fever at 100 µg following the second dose. This is of particular interest as the Sponsor considers the proposed study in adolescents as well as future studies in younger children. While no participants reported fever after the first injection, after the second injection, fever was reported in 6/15 (40%) in the 100 mg group and 8/14 (57%) in the 250 mg group. Only one febrile event was severe (Grade 3) – a participant in the 250 mg group. Two additional participants (21%) in the 250 µg dose group reported one or more severe solicited ARs. One participant in the 25 µg group was withdrawn from the study because of an unsolicited AE, transient urticaria, judged to be related to the first injection. Data on 40 older adults > 55 years of age who received 2 doses of either 25 or 100 µg in the same Phase 1 DMID study were recently published (Anderson et al 2020). After the second injection, serum neutralizing activity was detected in all participants by multiple methods with binding and nAb titers similar to those reported in adults 18 to 55 years of age and above the median for convalescent serum. Solicited ARs were predominantly mild or moderate in severity and most frequently included fatigue, chills, headache, myalgia, and pain at the injection site. Specifically regarding fever, no participant reported fever of any severity following the first injection. Following the second injection, 2 participants, in the 100 µg dose group reported fever categorized as mild. All participants have been vaccinated, and safety and immunogenicity follow-up is ongoing.

Additionally, an ongoing, placebo-controlled, dose-finding Phase 2a study (mRNA-1273-P201; NCT04405076) conducted by the Sponsor under IND 19745 aims to evaluate the safety, reactogenicity, and immunogenicity of mRNA-1273, administered as 2 doses 28 days apart at dose levels of 50 and 100 µg. The study is being conducted in 600 healthy adults in 2 age cohorts: 18 to 54 years of age (300 participants) and at least 55 years of age (300 participants). A safety monitoring committee reviewed the accumulated safety data after 1 of 2 doses on 25 Jun 2020 and after both doses on 05 Aug 2020 and recommended that the study continue enrollment and conduct. The study is now completely enrolled and all dosing is complete; participants are undergoing additional serologic testing and safety follow-up.

Lastly, the Sponsor has completed enrollment of a Phase 3, randomized, stratified, observer-blind, placebo-controlled study to evaluate the efficacy, safety, and immunogenicity of mRNA-1273 vaccine in adults (mRNA-1273-P301; NCT04470427) under IND 19745. The dose regimen of mRNA-1273 vaccine is an initial dose of 100 µg followed by a second dose of 100 µg 28 days later. As of 22 Oct 2020, the study was completely enrolled. All 30,000 participants had received their initial dose and more than 25,000 participants had received their second dose. Participants will be monitored for 13 months after their second dose to enable assessment of long-term safety and durability of vaccine efficacy.

A detailed review of the clinical experience with LNPs containing SM-102 (mRNA vaccines and placebo) is provided in the IB.

1.3. Benefit/Risk Assessment

1.3.1. Potential Benefits from Participation

The following benefits may accrue to participants:

- The mRNA-1273 vaccine may be an effective vaccine against COVID-19.
- Participants will have a baseline (Day 1) evaluation for SARS-CoV-2 infection and ongoing surveillance for COVID-19 throughout the study.
- The study will contribute to the development of a vaccine against COVID-19 for adolescents.

1.3.2. Risks from Study Participation and Their Mitigation

Immediate systemic allergic reactions (eg, anaphylaxis) can occur following any vaccination. These reactions are very rare and are estimated to occur once per 450,000 vaccinations for vaccines that do not contain allergens such as gelatin or egg protein (Zent et al 2002). As a precaution, all participants will remain under observation at the study site for at least 60 minutes after injection.

Vasovagal syncope (fainting) can occur before or after any vaccination, is usually triggered by the pain or anxiety caused by the injection, and is not related to the substance injected. Therefore, it is important that standard precautions and procedures are followed to avoid injury from fainting.

Intramuscular injection with other mRNA vaccines manufactured by the Sponsor containing the SM-102 lipid formulation commonly results in a transient and self-limiting local inflammatory reaction. This typically includes pain, erythema (redness), or swelling (hardness) at the injection site, which are mostly mild to moderate in severity and usually occur within 24 hours of injection.

The majority of local and systemic solicited ARs observed after injection with mRNA-1273 at the 100 µg dose level have been mild to moderate in severity (Section 1.2.2). The most commonly reported systemic ARs were headache, myalgia, fatigue, chills, and fever. In the majority of cases, the reactions resolved spontaneously within several days.

Laboratory abnormalities (including increases in liver function tests and serum lipase levels) following injection were observed in clinical studies with similar mRNA-based vaccines. These abnormalities were without clinical symptoms or signs and returned toward baseline (Day 1) values over time. The clinical significance of these observations is unknown. Further details are provided in the current IB.

There is a theoretical risk that active vaccination to prevent SARS-CoV-2 infection may cause a paradoxical increase in the risk of COVID-19. This possibility is based on the rare phenomenon of vaccine-associated disease enhancement, which was first seen in the 1960s with 2 vaccines made in the same way (formalin-inactivated whole virus) and designed to protect children against infection with respiratory syncytial virus (Chin et al 1969) or measles virus (Fulginiti et al 1967). Disease enhancement has also been proposed as a possible explanation for cases of more serious disease associated with dengue vaccination (Thomas and Yoon 2019; WHO 2019). It is not known if mRNA-1273 will increase the risk of enhanced disease.

In order to address this theoretical risk, animal studies were performed in young and aged wild-type mice and rhesus macaques (NHPs). These studies were designed to capture immunogenicity endpoints that would be predictive of enhanced respiratory disease (ERD) and also to evaluate if, at protective or subprotective dose levels of mRNA-1273, evidence of disease enhancement would be observed after challenge of the animals with SARS-CoV-2. These nonclinical studies demonstrated that mRNA-1273 is safe and well-tolerated in different animal species, is immunogenic; drives a robust SARS-CoV-2-specific antibody(Ab), neutralization, and T helper cell (Th1)-directed cluster of differentiation (CD)4 T-cell response; fully protects animals from challenge at dose levels as low as 1 μg/dose in mice and 30 μg/dose in NHPs; and does not lead to ERD at protective or subprotective dose levels (Corbett et al 2020a; Corbett et al 2020b). Clinical immunogenicity data from the DMID Phase 1 study of mRNA-1273 demonstrated high levels of nAbs and Th1-polarized CD4+ T-cell responses (Jackson et al 2020), consistent with the immunogenicity observed in these nonclinical studies. These data suggest that a paradoxical increase in the risk of disease, while not eliminated, is likely to be low.

1.3.3. Overall Benefit/Risk Conclusion

All participants will receive a single dosage of 100 μg of mRNA-1273 vaccine or placebo administered in 2 doses 28 days apart (Section 3.1).

Safety will be monitored throughout the study (Section 7.5).

Considering the lack of approved vaccines for COVID-19, the participants' risk of COVID-19 outside the study during a pandemic, and the nonclinical and clinical data to date, the Sponsor considers the potential benefits of participation to exceed the risks.

2. OBJECTIVES AND ENDPOINTS

The objectives which will be evaluated in this study and endpoints associated with each objective are provided in Table 1.

Table 1: Study Objectives and Endpoints

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the safety and reactogenicity of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart	• Solicited local and systemic ARs through 7 days after each injection • Unsolicited AEs through 28 days after each injection • MAAEs through the entire study period • SAEs through the entire study period • AESI of MIS-C through the entire study period • Vital sign measurements • Physical examination findings
• To infer efficacy of mRNA-1273 (100 µg, 2 doses 28 days apart), serum Ab responses obtained 28 days after the second injection of mRNA-1273 (Day 57) will be either: – Evaluated against an accepted Ab threshold of protection against COVID-19 (if established in Study P301) – Compared to GM values of serum Ab obtained from adult recipients of mRNA-1273 in the clinical endpoint efficacy trial (Study P301)	• The proportion of participants with a serum Ab level at Day 57 ≥ an Ab threshold of protection[1] • The GM value of serum nAb level from Study P203 vaccine recipients at Day 57 compared with the GM value of serum nAb level obtained from adult vaccine recipients (Day 57) in the clinical endpoint efficacy trial (Study P301)[2] 1. If an accepted serum nAb threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy 2. If a threshold is not available, efficacy will be inferred based on establishing noninferiority of adolescent (12 to < 18 years; this clinical study) to adult GM values of serum nAb obtained in Study P301 (GM value 12 to < 18 years / GM value ≥ 18 years).

Objectives	Endpoints
Secondary Objectives	**Secondary Endpoints**
• To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 μg) administered in 2 doses 28 days apart, as assessed by the level of SARS-CoV-2 S2P-specific bAb through 1 year after dose 2	• The GM value of SARS-CoV-2 S2P-specific bAb on Day 1, Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2)
• To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 μg) administered in 2 doses 28 days apart, as assessed by the level of nAb through 1 year after dose 2	• The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2)
• To evaluate the effect of mRNA-1273 on the incidence of SARS-CoV-2 infection compared with the incidence among placebo recipients	• The incidence of SARS-CoV-2 infection starting on Day 57 among recipients of mRNA-1273 and placebo will be compared • SARS-CoV-2 infection will be defined by detection of Ab against a nonvaccine antigen (eg, nucleocapsid protein); the definition of infection is dependent on baseline serostatus: – Participants seronegative at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein either from below the LOD or LLOQ at Day 1 that increase to above or equal to LOD or LLOQ starting at Day 57 or later. – Participants seropositive at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein above the LOD or LLOQ at Day 1 that increase by 4-fold or more in participants with pre-existing bAb starting at Day 57 or later.

Objectives	Endpoints
• To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with SARS-CoV-2 infection AND positive RT-PCR for SARS-CoV-2	• Vaccine efficacy of mRNA-1273 to prevent the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 is defined as symptomatic disease based on the following criteria: – The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥ 100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR – The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND – The participant must have at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR
Exploratory Objectives	**Exploratory Endpoints**
• To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence	• Alignment of genetic sequence of viral isolates with that of the vaccine sequence
• To describe the ratio or profile of specific bAb relative to nAb in serum	• Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum
• To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection	• Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19)

Abbreviations: Ab = antibody; AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; bAb = binding antibody; COVID 19 = coronavirus disease 2019; GM = geometric mean; IP = investigational product; LLOQ = lower limit of quantification; LOD = limit of detection; MAAE = medically attended adverse event; MIS-C = multisystem inflammatory syndrome in children; nAb = neutralizing antibody; NP = nasopharyngeal; RT-PCR = reverse transcriptase polymerase chain reaction; S = spike; S2P = S protein; SAE = severe adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

3. STUDY DESIGN

3.1. General Design

This is a Phase 2/3, randomized, observer-blind, placebo-controlled study intended to infer the effectiveness of mRNA-1273 in an adolescent population aged 12 to < 18 years. The study includes 2 arms: (i) 100 µg of mRNA-1273, and (ii) placebo. Approximately, 3,000 participants between 12 to < 18 years of age will be randomly assigned in a 2:1 ratio to receive mRNA-1273 (n=2,000) or placebo (n=1,000).

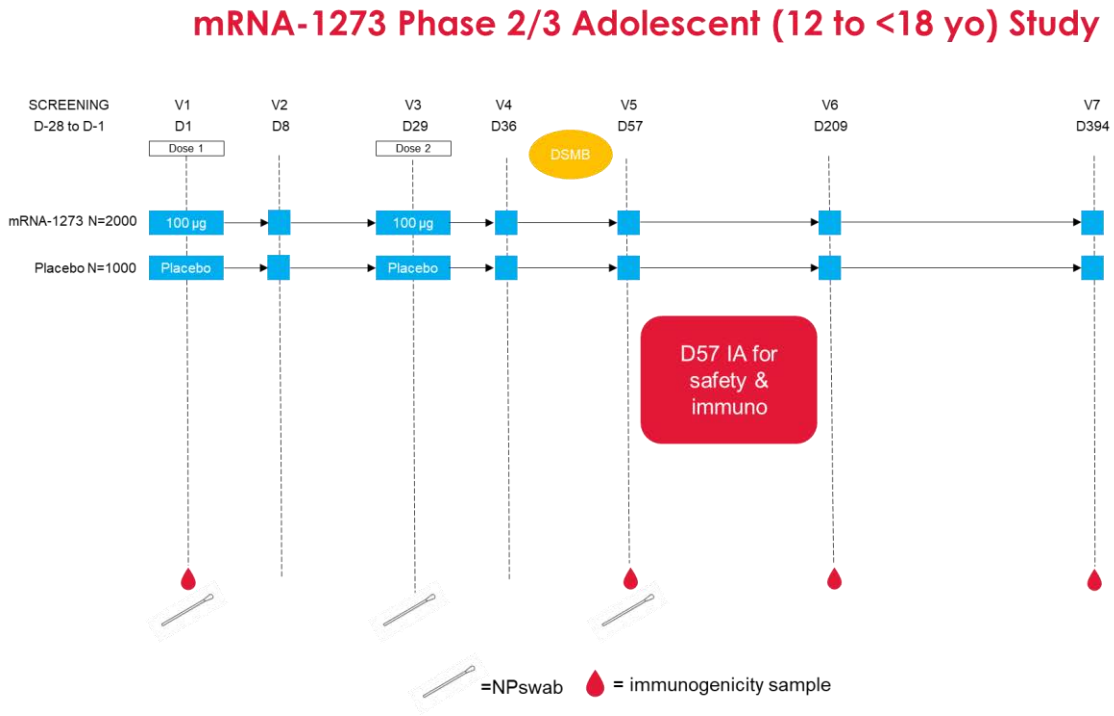
The schematic of study arms and major study events is illustrated in Figure 1.

The goal of the study is to seek an indication for use of mRNA-1273 (100 µg IM, given as 2 injections, 28 days apart) in the 12 to < 18 years age group. The basis for demonstrating vaccine effectiveness is proposed to be met by serum Ab response measured in this adolescent age group. The approach to inferring vaccine effectiveness will depend on whether an accepted serum Ab threshold conferring protection against COVID-19 has been established. If an Ab threshold of protection has been established, effectiveness will be inferred based on the proportion of adolescent study participants with serum Ab levels (on Day 57) that meet or exceed the Ab threshold. If an Ab threshold of protection has not been established, effectiveness will be inferred based on demonstrating noninferiority of the geometric mean (GM) value of serum nAb from adolescent participants compared with the GM value of serum nAb from adults enrolled in the ongoing clinical endpoint efficacy trial (Study P301). The statistical parameters to infer effectiveness are described in Section 2.

This study in adolescents will monitor all participants for a total of 12 months following the second dose of vaccine or placebo. Safety assessments will include solicited ARs (7 days after each injection), unsolicited AEs (28 days after each injection), medically attended adverse events (MAAEs), SAEs, and adverse events of special interest (AESIs) (multisystem inflammatory syndrome in children [MIS-C]) throughout the study period.

Blood samples will be collected from all participants at baseline (Day 1), Day 57 (28 days after dose 2), Day 209 (6 months after dose 2), and Day 394 for measurement of SARS-CoV-2-specific binding and nAb responses. Blood samples will also be tested for the development of Ab directed against non-vaccine antigen (eg, Ab against the nucleocapsid protein), which will signify infection with SARS-CoV-2. The incidence of SARS-CoV-2 infection among vaccine recipients and placebo recipients will be compared to assess the potential for mRNA-1273 to reduce the rate of infection in vaccine recipients.

Figure 1: Study Schema



Abbreviation: D = day; DSMB = Data Safety Monitoring Board, IA = interim analysis, immuno = immunogenicity, NP = nasopharyngeal, V = visit, yo = years old.

3.1.1. Study Periods

This study comprises 8 scheduled visits including a screening visit and 7 scheduled visits, of which Visit 2 and Visit 4 will be virtual/telephone visits and the other visits will be in-clinic visits.

The study duration will be approximately 14 months, which includes 1 month for screening (Day -28 to Day 1), 1 month for dosing (on Day 1 and Day 29), and 12 months of follow-up after the second dose to monitor for safety, immunogenicity, and efficacy.

Note: Day 0 and Day 1 may be combined on the same day (Table 6).

This study will be conducted in compliance with the protocol, Good Clinical Practice (GCP), and all applicable regulatory requirements (Section 10.2.1).

3.1.1.1. Screening Period

After providing informed consent/assent, participants will undergo screening assessments to determine study eligibility. Screening assessments (Table 6) must be completed after signing the informed consent form (ICF)/assent form. The investigator will review study entry criteria to determine the participant eligibility during the Screening Period.

Eligible participants will enter the Treatment Period.

3.1.1.2. Treatment and Follow-up Period

On Day 1, after the completion of the scheduled assessments (Table 6), participants will be administered a single IM dose of mRNA-1273 (100 µg) or placebo (procedures will be detailed in the mRNA-1273-P203 Pharmacy Manual). Participants will be closely monitored for safety and will remain at the study site for observation for at least 60 minutes after dosing. On Day 29 the second dose of investigational product (IP) will be administered. Participants will be monitored for 12 months after the second dose of IP for safety and immunogenicity assessments.

To test for the presence of SARS-CoV-2 by RT-PCR, nasopharyngeal (NP) swab samples will be collected on each day of injection prior to dosing and on Day 57 (28 days postdose 2), according to the schedule of assessments (SoA, Table 6).

During the course of the study, participants who meet prespecified disease criteria that suggest possible SARS-CoV-2 infection will be asked to contact the study site to arrange for a prompt, thorough, and careful assessment, including an NP swab sample to be tested for the presence of SARS-CoV-2 by RT-PCR. Confirmed, symptomatic cases of SARS-CoV-2 infection will be captured as MAAEs and reported in an expedited time frame to the Sponsor (Section 7.3.3).

All participants will be monitored for safety and reactogenicity and provide pre- and postdose blood specimens for immunogenicity through 12 months after the second dose of mRNA-1273.

Participants will be instructed on the day of the first dose (Day 1) and reminded on the day of the second dose (Day 29) how to document and report solicited local or systemic ARs in a provided electronic diary (eDiary). Solicited ARs, unsolicited AEs, MAAEs, AEs leading to withdrawal, AESIs, and SAEs will be assessed as described in Section 7.1, according to the time points in the SoA (Table 6).

Blood sampling for immunogenicity testing is scheduled throughout the study: on the day of injection before the first dose and 1, 6, and 12 months after the second dose.

Participants may experience AEs that necessitate an unscheduled visit, including situations when the investigator asks a participant to return to the study clinic for an unscheduled visit following the report of an AE. Additional examinations may be conducted at these visits as necessary to ensure the safety and well-being of participants during the study. Electronic case report forms (eCRFs) should be completed for each unscheduled visit.

3.2. Scientific Rationale for Study Design

The single age cohort in this Phase 2/3 study, 12 to < 18 years of age, was established to understand the tolerability and immunogenicity of mRNA-1273 in an adolescent population. The lower age boundary used in this study is consistent with the definition of adolescence provided by the American Academy of Pediatrics (Hardin et al 2017). Knowledge of the tolerability of

mRNA-1273 in adolescent participants will be critical before proceeding to future studies in younger children.

With SARS-CoV-2 expected to be circulating in the general population during the study, all participants will provide pre-injection blood samples and postinjection blood samples for Ab analysis through 12 months after the last dose of IP. In addition, participants will have NP swab samples collected, before the injections on Day 1 and Day 29, and on Day 57. Furthermore, with any signs or symptoms or MAAE suggesting SARS-CoV-2 infection in a participant, an additional nasal or NP swab sample and a blood sample will be taken to confirm the diagnosis of SARS-CoV-2 via serology and RT-PCR. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.

As it is possible that participants are naturally exposed to SARS-CoV-2 through community exposure, the NP and/or nasal swab samples collected before study injection and the serologic assays for Ab responses to nonvaccine antigen(s) may help discriminate between natural infection and vaccine-induced Ab responses, should such discrimination be needed.

3.3. Justification for Dose, Control Product, and Choice of Study Population

The 100 μg dose level is currently being investigated in a large Phase 3 efficacy study in adults 18 years of age and older; therefore, based on this and the results of the studies described in Section 1.2.2, the Sponsor intends to study a single dose level of 100 μg in this Phase 2/3 study in the adolescents age group of 12 to < 18 years of age.

As there are currently no licensed SARS-CoV-2 vaccines available, 0.9% sodium chloride will be used as a placebo control for the safety and immunogenicity assessments. Consequently, the mRNA-1273 vaccine and placebo injections will look different, so administration will be blinded (Section 8.1).

3.4. End-of-Study Definition

The end-of-study (EOS) for the full study is defined as completion of the last visit of the last participant in the study or the last scheduled procedure as shown in the SoA (Table 6) for the last participant in this study.

4. STUDY POPULATION

Participants will be enrolled at approximately 15 to 25 study sites in the United States or its territories.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria

Each participant must meet all of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, to be enrolled in this study:

1. Male or female, 12 to < 18 years of age at the time of consent (Screening Visit, Day 0) who, in the opinion of the investigator, is in good general health based on review of medical history and screening physical examination.
2. Investigator assessment that the participant, in the case of an emancipated minor, or parent(s)/legally acceptable representative(s) [LAR(s)] understand and are willing and physically able to comply with protocol-mandated follow-up, including all procedures and provides written informed consent/assent.
3. Body mass index (BMI) at or above the third percentile according to WHO Child Growth Standards at the Screening Visit (Day 0) see Section 10.2.18.
4. Female participants of nonchildbearing potential may be enrolled in the study. Nonchildbearing potential is defined as premenarche or surgically sterile (history of bilateral tubal ligation, bilateral oophorectomy, hysterectomy).
5. Female participants of childbearing potential may be enrolled in the study if the participant fulfills all the following criteria:
    - Has a negative pregnancy test at Screening (Day 0), on the day of the first injection (Day 1), and on the day of the second injection (Day 29)
    - Has practiced adequate contraception or has abstained from all activities that could result in pregnancy for at least 28 days prior to the first injection (Day 1)
    - Has agreed to continue adequate contraception through 3 months following the second injection (Day 29)
    - Is not currently breastfeeding.

Adequate female contraception is defined as consistent and correct use of a US Food and Drug Administration (FDA)-approved contraceptive method in accordance with the product label (Section 10.3).

4.2. Exclusion Criteria

Participants who meet any of the following criteria at the Screening Visit (Day 0) or at Day 1, unless noted otherwise, will be excluded from the study:

1. Known history of SARS-CoV-2 infection or known close contact with anyone with laboratory-confirmed SARS-CoV-2 infection or COVID-19 within 2 weeks prior to vaccine administration.
2. Travel outside of the United States in the 28 days prior to the Screening Visit (Day 0).
3. Pregnant or breastfeeding.
4. Is acutely ill or febrile 24 hours prior to or at the Screening Visit (Day 0). Fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F. Participants who meet this criterion may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
5. Prior administration of an investigational CoV (eg, SARS-CoV-2, SARS-CoV, MERS-CoV) vaccine.
6. Current treatment with investigational agents for prophylaxis against COVID-19.
7. Has a medical, psychiatric, or occupational condition that may pose additional risk as a result of participation, or that could interfere with safety assessments or interpretation of results according to the investigator's judgment.
8. Current use of any inhaled substance (eg, tobacco or cannabis smoke, nicotine vapors).
9. History of chronic smoking (≥ 1 cigarette a day) within 1 year of the Screening Visit (Day 0).
10. History of illegal substance use or alcohol abuse within the past 2 years. This exclusion does not apply to historical cannabis use that was formerly illegal in the participant's state but is legal at the time of screening.
11. History of a diagnosis or condition that, in the judgment of the investigator, may affect study endpoint assessment or compromise participant safety, specifically:
    - Congenital or acquired immunodeficiency, including human immunodeficiency virus (HIV) infection
    - Suspected active hepatitis
    - Has a bleeding disorder that is considered a contraindication to IM injection or phlebotomy
    - Dermatologic conditions that could affect local solicited AR assessments

- History of anaphylaxis, urticaria, or other significant AR requiring medical intervention after receipt of a vaccine
- Diagnosis of malignancy within the previous 10 years (excluding nonmelanoma skin cancer)
- Febrile seizures

12. Receipt of:
    - Any licensed vaccine within 28 days before the first dose of IP or plans for receipt of any licensed vaccine through 28 days following the last dose of IP
    - Systemic immunosuppressants or immune-modifying drugs for > 14 days in total within 6 months prior to the day of enrollment (for corticosteroids, ≥ 20 mg/day prednisone equivalent). Topical tacrolimus is allowed if not used within 14 days prior to the day of enrollment. Participants may have visits rescheduled for enrollment if they no longer meet this criterion within the Screening Visit window. Inhaled, nasal, and topical steroids are allowed.
    - Intravenous blood products (red cells, platelets, immunoglobulins) within 3 months prior to enrollment
13. Has donated ≥ 450 mL of blood products within 28 days prior to the Screening Visit (Day 0) or plans to donate blood products during the study.
14. Participated in an interventional clinical study within 28 days prior to the Screening Visit (Day 0) or plans to do so while participating in this study.
15. Is an immediate family member or has a household contact who is an employee of the research center or otherwise involved with the conduct of the study.

4.3. Lifestyle Restrictions

Participants must not eat or drink anything hot or cold within 10 minutes before oral temperature is taken.

4.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to treatment. A minimum set of screen failure information is required to ensure transparent reporting of screen failures to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimum information includes date of informed consent, demography, reason(s) for

screen failure, eligibility criteria, and information on any SAE that may have occurred from Day 1 to the time of withdrawal.

5. STUDY TREATMENT

5.1. Investigational Product Administered

The term IP refers to mRNA-1273 (100 μg) vaccine or placebo (0.9% sodium chloride) in this study.

The mRNA-1273 is an LNP dispersion of an mRNA encoding the prefusion stabilized S protein of SARS-CoV-2 formulated in LNPs composed of 4 lipids (1 proprietary and 3 commercially available): the proprietary ionizable lipid SM-102; cholesterol; 1,2-distearoyl-sn-glycero-3-phosphocholine (DSPC); and 1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol with polyethylene glycol of average molecular weight 2000 (1-monomethoxypolyethyleneglycol-2,3-dimyristylglycerol polyethylene glycol 2000 [PEG2000-DMG]). mRNA-1273 injection is provided as a sterile liquid for injection, white to off-white dispersion in appearance, at a concentration of 0.5 mg/mL in 20 mM Tris buffer containing 87 mg/mL sucrose and 10.7 mM sodium acetate at pH 7.5.

5.2. Randomization

Random assignment of participants will use a centralized interactive response technology (IRT), in accordance with pregenerated randomization schedules.

5.3. Dosing and Management of mRNA-1273 Vaccine

5.3.1. Preparation of Study Vaccine for Injection

Each dose of IP will be prepared for each participant based on the assigned treatment, as detailed in the mRNA-1273-P203 Pharmacy Manual. The volume of IP injected will be 0.5 mL consisting of either 100 μg dose of mRNA-1273 or placebo (normal saline), as detailed in the mRNA-1273-P203 Pharmacy Manual.

5.3.2. Administration of Study Vaccine

Each participant will receive 2 doses of IP by IM injection, 28 days apart (ie, Day 1 and Day 29) into the deltoid muscle, according to their assigned regimen and according to the procedures specified in the mRNA-1273-P203 Pharmacy Manual. Preferably, both doses should be administered into the nondominant arm.

At each visit when IP is administered, participants will be monitored for a minimum of 60 minutes after administration. Assessments will include vital sign measurements and monitoring for local or systemic reactions (SoA, Table 6).

Eligibility for a subsequent dose of IP will be determined by following the criteria outlined in Section 6.

The study sites will be appropriately staffed with individuals with basic cardiopulmonary resuscitation training/certification. Either on-site resuscitation equipment and personnel or appropriate protocols for the rapid transport of participant to a resuscitation area or facility are required.

5.3.3. Study Vaccine Delivery and Receipt

The Sponsor or designee is responsible for the following:

- Supplying the IP
- Confirming the appropriate labeling of the IP, so that it complies with the legal requirements of the United States

The investigator is responsible for acknowledging the receipt of the IP by a designated staff member at the study site, including the following:

- Confirming that the IP was received in good condition
- Confirming that the temperature during shipment from the Sponsor to the investigator's designated storage location was appropriate
- Confirming that the Sponsor has authorized the IP for use
- Ensuring the appropriate dose level of IP is properly prepared using aseptic technique

Further description of the IP and instructions for the receipt, storage, preparation, administration, accountability, and destruction of the IP are described in the mRNA-1273-P203 Pharmacy Manual.

5.3.4. Study Vaccine Packaging and Labeling

The Sponsor will provide the investigator (via the study site pharmacy) with adequate quantities of IP. The sterile IP is packaged in 10R glass vials with a 5.0-mL fill volume. The IP will have all required labeling per regulations and will be supplied to the pharmacy in an unblinded manner.

The IP will be packaged and labeled in accordance with the standard operating procedures of the Sponsor or of its designee, Code of Federal Regulations (CFR) Title 21, Good Manufacturing Practice guidelines, International Council for Harmonisation (ICH) GCP guidelines, guidelines for Quality System Regulations, and applicable regulations.

5.3.5. Study Vaccine Storage

The IP must be stored at 2°C to 8°C in a secure area with limited access and protected from moisture and light until it is prepared for administration (Section 5.3.1). The refrigerator should have automated temperature recording and a 24-hour alert system in place that allows for rapid response in case of refrigerator malfunction. There must be an available backup refrigerator. The

refrigerators must be connected to a backup generator. In addition, IP accountability study staff are required to keep a temperature log to establish a record of compliance with these storage conditions. The study site is responsible for reporting any IP that was not temperature controlled during shipment or during storage. Such IP will be retained for inspection by the monitor and disposed of according to approved methods.

5.3.6. Study Vaccine Accountability

It is the investigator's responsibility that the IP accountability study staff maintain accurate records in an IP accountability log of receipt of all IP, study site IP inventory, IP dispensing, IP injections, and return to the Sponsor or alternative disposition of used and unused IP vials.

A study site monitor will review the inventory and accountability log during study site visits and at the completion of the study. Additional details are found in the mRNA-1273-P203 Pharmacy Manual.

5.3.7. Study Vaccine Handling and Disposal

A study site monitor will reconcile the IP inventory during the conduct and at the end of the study for compliance. Once fully reconciled at the study site at the end of the study, the IP can be destroyed at the investigational site or at a Sponsor-selected third party, as appropriate.

Vaccine may be destroyed at the study site only if permitted by local regulations and authorized by the Sponsor. A certificate of destruction must be completed and sent to the Sponsor or designee.

5.4. Study Treatment Compliance

All doses of IP will be administered at the study site under direct observation of medically qualified study staff and appropriately recorded (date and time) in the eCRF. Qualified study site staff will confirm that the participant has received the entire dose of IP. If a participant does not receive IP or does not receive all of the planned dose, the reason for the missed dose will be recorded. Data will be reconciled with study site accountability records to assess compliance.

Participants who miss the second dose due to noncompliance with the visit schedule and not due to a safety pause will still be required to follow the original visit and testing schedule as described in the protocol and their regimen schedule. Unless consent is withdrawn, a participant who withdraws or is withheld from receiving the second dose will remain in the study and complete all safety and immunogenicity assessments required through the participant's last scheduled study visit.

The study site staff are responsible for ensuring that participants comply with the allowed study visit windows. If a participant misses a visit, every effort should be made to contact the participant and complete a visit within the defined visit window (SoA, Table 6). If a participant does not

complete a visit within the time window, that visit will be classified as a missed visit and the participant will continue with subsequent scheduled study visits. All safety requirements of the missed visit will be captured and included in the subsequent visit.

5.5. Prior and Concomitant Medications

5.5.1. Prior Medications and Therapies

Information about prior medications (including any prescription or over-the-counter medications, vaccines, or blood products) taken by the participant within the 28 days before providing informed consent/assent (or as designated in the inclusion/exclusion requirements) will be recorded in the participant's eCRF.

5.5.2. Concomitant Medications and Therapies

At each study visit, study site staff must question the participant and/or the participants' parent(s)/LAR(s) regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All nonstudy vaccinations administered within the period starting 28 days before the first dose of IP.
- All concomitant medications and nonstudy vaccinations taken through 28 days after each dose of IP. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications relevant to or for the treatment of an SAE or a MAAE.
- Participants will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each dose of IP, including the day of injection. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the postinjection study visits or via other participant interactions (eg, telephone calls).

5.5.3. Recording of Concomitant Medications and Concomitant Vaccinations

Study site staff must question the participant regarding any medications taken and vaccinations received by the participant and record the following information in the eCRF:

- All nonstudy vaccinations administered within the period starting 28 days before the first dose of IP.
- Seasonal influenza vaccine administered for the current influenza season (typically October through April in the Northern Hemisphere).

- All concomitant medications and nonstudy vaccinations taken through 28 days after each dose of IP. Antipyretics and analgesics taken prophylactically (ie, taken in the absence of any symptoms in anticipation of an injection reaction) will be recorded as such.
- Any concomitant medications used to prevent or treat COVID-19 or its symptoms.
- Any concomitant medications relevant to or for the treatment of an SAE or a MAAE.
- Participants will be asked in the eDiary if they have taken any antipyretic or analgesic to treat or prevent fever or pain within 7 days after each IP dose, including on the day of dosing. Reported antipyretic or analgesic medications should be recorded in the source document by the study site staff during the postinjection study visits or via other participant interactions (eg, phone calls).

Concomitant medications (including vaccinations) will be coded using the WHO Drug Dictionary. If a participant takes a prohibited drug therapy, the investigator and the contract research organization's (CRO's) medical monitor will make a joint decision about continuing or withholding further injection of the participant based on the time the medication was administered, the drug's pharmacology and pharmacokinetics, and whether use of the medication will compromise the participant's safety or interpretation of the data. It is the investigator's responsibility to ensure that details regarding the concomitant medications are adequately recorded in the eCRF.

5.5.4. Concomitant Medications and Vaccines that May Lead to the Elimination of a Participant from Per-Protocol Analyses

The use of the following concomitant medications and/or vaccines will not require withdrawal of the participant from the study but may determine a participant's eligibility to receive a second dose or evaluability in the per-protocol (PP) analysis (analysis sets are described in Section 8.4):

- Any investigational or nonregistered product (drug or vaccine) other than the IP used during the study period.
- Immunosuppressants or other immune-modifying drugs administered chronically (ie, more than 14 days in total) during the study period. For corticosteroids, this will mean that prednisone ≥ 20 mg/day or the equivalent is not permitted. Inhaled, nasal, and topical steroids are allowed.
- Long-acting immune-modifying drugs administered at any time during the study period (eg, infliximab).
- Immunoglobulins and/or any blood products administered during the study period.

5.6. Intervention After the End of the Study

Any SAE occurring after the end of the study and considered to be caused by the IP must be reported to the Sponsor.

6. DELAYING OR DISCONTINUING STUDY TREATMENT AND PARTICIPANT WITHDRAWAL FROM THE STUDY

6.1. Criteria for Delay of Vaccine Administration

6.1.1. Individual Participant Criteria for Delay of Study Vaccination

Body temperature (oral) must be measured on dosing visits before vaccine administration. The following events constitute criteria for delay of injection, and if either of these events occur at the time scheduled for dosing, the participant may receive the study injection at a later date within the time window specified in the relevant SoA (Table 6), or the participant may be discontinued from dosing at the discretion of the investigator (Section 6.2):

- Acute moderate or severe infection with or without fever at the time of dosing
- Fever, defined as body temperature ≥ 38.0°C/≥ 100.4°F at the time of dosing

Participants with a minor illness without fever, as assessed by the investigator, can be vaccinated. Participants with a fever of ≥ 38.0°C/≥ 100.4°F will be contacted within the time window acceptable for participation and re-evaluated for eligibility. If the investigator determines that the participant's health on the day of dosing temporarily precludes injection, the visit should be rescheduled within the allowed interval for that visit.

If a participant takes a prohibited drug therapy, an injection could be delayed within the visit window based on the joint decision of the investigator and the CRO's medical monitor (Section 5.5.3).

6.2. Discontinuing Study Vaccination

Participants can discontinue study injection (ie, refuse the second dose) for any reason, without prejudice to further treatment the participant may need to receive.

The investigator, in consultation with the Sponsor's medical monitor, may withhold a participant from further injection if the participant experiences any of the following:

- Becomes pregnant
- Withdrawal of consent (not related to COVID-19)
- If either the serology or RT-PCR result from Day 1 is positive for SARS-CoV-2
- If an RT-PCR result from an illness visit (Section 7.1.6) is positive for SARS-CoV-2
- Develops, during the course of the study, symptoms or conditions listed in the exclusion criteria (Section 4.2).

- Experiences an AE (other than reactogenicity) after injection that is considered by the investigator to be related to IP (Section 7.4.9) and is of Grade 3 (severe) or greater severity
- Experiences an AE or SAE that, in the judgment of the investigator, requires IP withdrawal due to its nature, severity, or required treatment, regardless of the causal relationship to vaccine
- Experiences an AESI (MIS-C)
- Experiences a clinically significant change in vital sign measurements, or general condition that, in the judgment of the investigator, requires vaccine withdrawal
- Experiences anaphylaxis clearly related to IP
- Experiences generalized urticaria related to IP

The reason(s) for withdrawal from further injection will be recorded in the eCRF.

If a participant takes a prohibited drug therapy, the investigator could withhold the second dose based on a joint decision of the investigator and the CRO's medical monitor (Section 5.5.3).

Every reasonable attempt will be made to follow up with participants for safety throughout the entire scheduled study period according to their regimen, even if the participant does not receive the second dose or misses one or more visits. Unless participants withdraw consent, they are expected to remain in the study and complete all scheduled visits and assessments.

6.3. Participant Discontinuation/Withdrawal from the Study

Participants who withdraw or are withdrawn from the study will not be replaced. A "withdrawal" from the study refers to a situation wherein a participant does not return for the final visit planned in the protocol. The statistical management of participant withdrawals is discussed in Section 8.

Participants can withdraw consent and withdraw from the study at any time, for any reason, without prejudice to further treatment the participant may need to receive. The investigator will request that the participant complete all study procedures pending at the time of withdrawal.

If participant desires to withdraw from the study because of an AE, the investigator will try to obtain agreement to follow up with the participant until the event is considered resolved or stable and will then complete the EOS eCRF.

Information related to the withdrawal will be documented in the eCRF. The investigator will document whether the decision to withdraw a participant from the study was made by the participant or by the investigator, as well as which of the following possible reasons was responsible for withdrawal:

- AE (specify)
- SAE (specify)
- Death
- Lost to follow-up (LTFU)
- Physician decision (specify)
- Pregnancy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal of consent by participant (specify)
- Other (specify)

Participants who are withdrawn from the study because of AEs (including SAEs) must be clearly distinguished from participants who are withdrawn for other reasons. Investigators will follow up with participants who are withdrawn from the study as result of an SAE or AE until resolution of the event.

A participant who withdraws from the study may request destruction of any samples taken and not tested, and the investigator must document this in the study site study records.

If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent (Section 10.2.10).

The Sponsor will continue to retain and use all research data that have already been collected for the study evaluation, unless the participant has requested destruction of these samples. All biological samples that have already been collected may be retained and analyzed at a later date (or as permitted by local regulations).

6.4. Study Pause Rules

The investigators, study medical monitor, and Sponsor will monitor for events that could trigger a study pause. Study pause rule criteria, events, and thresholds are described in Table 2.

Table 2: Pause Rule Criteria, Events, and Thresholds

Pause Rule Criterion	Event	Participant Threshold for Triggering Study Pause
1	Any death due to SARS-CoV-2 infection	≥ 1
2	Any related SAE or related Grade 4 AE	≥ 1
3	Hospitalization due to SARS-CoV-2 infection	≥ 1
4[a]	Any Grade 3 solicited local AE lasting ≥ 24 hours and occurring within 7-days of injection (Days 1-8)	≥ 30 participants out of the first 300 participants enrolled
5[a]	Any Grade 3 solicited general AE lasting ≥ 24 hours and occurring within 7-days of injection (Days 1-8)	≥ 30 participants out of the first 300 participants enrolled
6[a]	Any ≥ Grade 3 unsolicited AE that cannot be reasonably attributed to a cause other than vaccination	≥ 30 participants out of the first 300 participants enrolled

Abbreviations: AE = adverse event; ICU = intensive care unit; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus.
[a] Pause Rules 4,5, and 6 apply only to the first 300 participants enrolled.

If any of the thresholds for a study pause is met, the Sponsor will immediately suspend further enrollment and/or study dosing by notifying all investigators. Such a suspension will remain in force until the threshold event(s) is (are) reviewed by the Data Safety Monitoring Board (DSMB) and a recommendation to continue is provided to the Sponsor.

The investigator or designee is responsible for reporting to the Sponsor, via the electronic data capture (EDC) system within 24 hours of observation, each event that potentially meets any pause rule criterion. The Sponsor will inform the DSMB of any event that potentially meets any pause rule criterion. The DSMB will review all available study data to adjudicate such events in accordance with the DSMB charter.

The Sponsor will notify the Center for Biologics and Evaluation Research (CBER) within 48 hours in the event of a study pause. In the event of a study pause, all safety and immunogenicity assessments will continue per protocol. The window allowance for injection visits may be extended by an additional 7 days (ie, +14 days) for affected participants at the discretion of the Sponsor.

6.5. Lost to Follow-up

A participant will be considered LTFU if he or she repeatedly fails to return for scheduled visits without stating an intention to withdraw consent and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The study site staff must attempt to contact the participant and reschedule the missed visit as soon as possible, counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.
- Before a participant is deemed LTFU, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts (eg, dates of telephone calls and registered letters) should be documented in the participant's medical record.
- A participant who continues to be unreachable or continues to be noncompliant with study visits or procedures will be considered to have withdrawn from the study.
- A participant should not be considered LTFU until due diligence has been completed.

7. STUDY ASSESSMENTS AND PROCEDURES

Before performing any study procedures, all potential participants and/or participants' parent/LAR will sign an ICF (as detailed in Section 10.2.6). Participants will undergo study procedures at the time points specified in the SoA (Table 6). A participant can also be seen for an unscheduled visit at any time during the study. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for COVID-19, or new or ongoing AEs. The study site also has the discretion to make reminder telephone calls or send text messages to inform the participant about visits, review eDiary requirements, or follow-up on ongoing or outstanding issues.

In accordance with "FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency" (DHHS 2020), investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor. Such action should be taken to protect the safety and well-being of study participants and study site staff or to comply with state or municipal mandates.

General considerations for study assessments and procedures include the following:

- Protocol waivers or exemptions are not allowed. The study procedures and their timing must be followed as presented in Table 6. Adherence to the study design requirements is essential and required for study conduct.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the participant should continue study treatment or participation in the study.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline assessments provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.

7.1. Safety Assessments and Procedures

Safety assessments will include monitoring and recording of the following for each participant, according to the SoA (Table 6):

- Solicited local and systemic ARs (Section 7.4.3) that occur during the 7 days following each injection (ie, the day of injection and 6 subsequent days). Solicited ARs will be recorded daily using eDiaries (Section 7.1.1).

- Unsolicited AEs observed or reported during the 28 days following each injection (ie, the day of injection and 27 subsequent days). Unsolicited AEs are defined in Section 7.4.1).
- AEs leading to discontinuation from dosing and/or study participation from Day 1 through the last day of study participation
- MAAEs from first dose on Day 1 through the entire study period
- SAEs from first dose on Day 1 through the entire study period
- AESI of MIS-C through the entire study period
- Vital sign measurements (Section 7.1.4)
- Physical examination findings (Section 7.1.5)
- Assessments for SARS-CoV-2 infection from Day 1 through study completion (Section 7.1.6).
- Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study (Section 7.4.6).

7.1.1. Use of Electronic Diaries

At the time of consent/assent, participants or their caregivers must confirm they will be willing to complete an eDiary using either an application downloaded to their smartphone or using a device that is provided at the time of enrollment. Before enrollment on Day 1, participants or their caregivers will be instructed to download the eDiary application or will be provided an eDiary device to record solicited ARs (Section 7.4.3) on Day 1.

At each injection visit, participants or their caregivers will be instructed (Day 1) or reminded (Day 29) on thermometer usage to measure body temperature, ruler usage to measure injection site erythema and swelling/induration (hardness), and self-assessment for localized axillary swelling or tenderness on the same side as the injection arm.

At each injection visit, participants or their caregivers will record data into the eDiary starting approximately 1 hour after injection under supervision of the study site staff to ensure successful entry of assessments. The study site staff will perform any retraining as necessary. Participants or their caregivers will continue to record data in the eDiary after they leave the study site, preferably in the evening and at the same time each day, on the day of injection and for 6 days following injection.

Participants or their caregivers will record the following data in the eDiary:

- Solicited local and systemic reactogenicity ARs, as defined in Section 7.4.3, that occur on the day of each vaccine administration and during the 7 days after vaccine administration

(ie, the day of injection and 6 subsequent days). If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until it is resolves or the next IP injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination and not to exceed 28 days after each vaccination, whichever occurs first. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit.

- Daily oral body temperature measurement should be performed at approximately the same time each day using the thermometer provided by the study site. If body temperature is taken more than once in a given day, only the highest temperature reading should be recorded.
- Measurement, as applicable, for solicited local ARs (injection site erythema and swelling/induration); the size measurements will be performed using the ruler provided by the study site.
- Any medications taken to treat or prevent pain or fever on a day of injection or for the next 6 days.

The eDiary will be the only source documents allowed for solicited systemic or local ARs (including body temperature measurements). Participants or their caregivers will be instructed to complete eDiary entries daily. The participant or their caregiver will have a limited window on the following day to complete assessments for the previous day; quantitative temperature recordings and measurement of any injection site erythema or swelling/induration reported on the following day may be excluded from the analyses of solicited ARs.

Any new safety information reported during safety telephone calls or at study site visits (including a solicited reaction) that is not already captured in the eDiary will be described in the source documents as a verbally reported event. An event reported in this manner must be described as a solicited event and entered on the solicited AR eCRF.

Study site staff will review eDiary data with participants at visits 7 days after each injection.

The eDiary will also be used every 4 weeks, starting at Day 71 through Day 183 and again starting at Day 223 through Day 363, to capture the occurrence of AEs, MAAEs, SAEs, AESI, or AEs leading to withdrawal. As specified in the applicable SoA (Table 6), the eDiary will prompt the participant to complete an eDiary questionnaire that collects the following data:

- Changes in health since last completing the questionnaire or since in contact with the study site

- Known exposure to someone with known COVID-19 or SARS-CoV-2 infection
- Any experience of symptoms of COVID-19
- Any MAAEs or SAEs

If an eDiary record results in identification of relevant safety events according to the study period, or of symptoms of COVID-19, a follow-up safety telephone call will be triggered.

Completion of eDiary questionnaires will alternate with safety telephone calls (Section 7.1.2) as the procedure for safety follow-up approximately every 4 weeks starting at Day 85 through Day 197 and again starting at Day 237 through Day 377 (SoA, Table 6).

7.1.1.1. Ancillary Supplies for Participant Use

Study sites will distribute Sponsor-provided oral thermometers and rulers for use by participants in assessing body temperature and injection site reactions for recording solicited ARs in eDiaries. Based on availability, smartphone devices may be provided to those participants who do not have their own device to use for eDiary activities.

7.1.2. Safety Telephone Calls

A safety telephone call is a telephone call made to the participant by trained study site personnel. This call will follow a script, which will facilitate the collection of relevant safety information. Safety telephone calls follow a schedule for each participant as indicated in the SoA (Table 6). The participant will be interviewed according to the script about occurrence of AEs, MAAEs, SAEs, AESI, AEs leading to study withdrawal, concomitant medications associated with those events, and any nonstudy vaccinations (Section 7.4.7). In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms. All safety information collected from the telephone contact must be documented in source documents as described by the participant and not documented on the script used for the safety telephone contact. As noted in Section 7.1.1, an unscheduled follow-up safety telephone call may be triggered if an eDiary record results in identification of a relevant safety event.

7.1.3. Safety Laboratory Assessments

No scheduled laboratory assessments for safety are planned. This is based on the absence of clinically significant abnormal laboratory findings in the Phase 1 and Phase 2 studies of mRNA-1273 in adults.

A point-of-care urine pregnancy test will be performed at the Screening Visit (Day 0) and before each vaccine dose. At any time, a pregnancy test either via blood or point-of-care urine can be performed, at the discretion of the investigator.

7.1.4. Vital Sign Measurements

Vital sign measurements will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature (preferred route is oral). The participant will be seated for at least 5 minutes before all measurements are taken. Vital signs will be measured at the time points indicated in the SoA (Table 6). At dosing visits, vital sign measurements will be collected once before injection and at least 1 hour post injection (before participants are discharged from the study site).

Febrile participants at dosing visits (fever is defined as a body temperature ≥ 38.0°C/≥ 100.4°F) may have visits rescheduled within the relevant study visit windows. Afebrile participants with minor illnesses may be injected at the discretion of the investigator.

When procedures overlap and are scheduled to occur at the same time point, the order of procedures should be vital sign measurements and then the blood collection.

7.1.5. Physical Examinations

A full physical examination, including height and weight, will be performed at scheduled time points as indicated in the SoA (Table 6). The full examination will include assessment of skin, head, ears, eyes, nose, throat, neck, thyroid, lungs, heart, cardiovascular system, abdomen, lymph nodes, and musculoskeletal system/extremities. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE.

Body mass index will be calculated at the Screening Visit (Day 0) only.

7.1.6. Assessment for SARS-CoV-2 Infection

Study participants will have NP samples collected for SARS-CoV-2 testing at time points specified in the SoA (Table 6).

A study illness visit or a consultation will be arranged within 72 hours or as soon as possible to collect an NP or nasal swab sample (NP is preferred) to ascertain the presence of SARS-CoV-2 via RT-PCR if a participant experiences any of the following:

- Signs or symptoms of SARS-CoV-2 infection as defined by the CDC (CDC 2020b)
- Exposure to an individual confirmed to be infected with SARS-CoV-2
- MAAE suggesting a SARS-CoV-2 infection

If the participant had known exposure to COVID-19 (eg, exposure to someone with confirmed COVID-19), it will be captured in the COVID-19 exposure form.

If scheduled, the study illness visit may collect additional clinical information, including assessments such as medical history, physical examination, blood sampling for clinical laboratory testing, and nasal, saliva, and/or NP swab sampling for viral PCR (including multiplex PCR for respiratory viruses including SARS-CoV-2) to evaluate the severity of the clinical case. Radiologic imaging studies may be conducted. All findings will be recorded in the eCRF.

If participants are confirmed to have SARS-CoV-2 infection, the investigator will notify the participant, and the participant's primary care physician, of the diagnosis. If the study participant does not have a primary care physician, the investigator will assist them to obtain one. The participant will also be instructed on infection prevention measures consistent with local public health guidance.

Any confirmed symptomatic SARS-CoV-2 infection occurring in participants will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.3). At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection.

7.2. Immunogenicity Assessments

Blood samples for immunogenicity assessments will be collected at the time points indicated in the SoA (Table 6): The following analytes will be measured:

- Serum nAb level against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays
- Serum binding antibody (bAb) against SARS-CoV-2 nucleocapsid protein measured by ligand-binding assay specific to the SARS-CoV-2 S protein
- Qualitative and quantitative measure of viral load against SARS-CoV-2 as measured by RT-PCR

Sample aliquots will be designed to ensure that backup samples are available and that vial volumes are likely to be adequate for future testing needs. The actual time and date of each sample collected will be recorded in the eCRF, and unique sample identification will be utilized to maintain the blind at the laboratory at all times and to allow for automated sample tracking and housing. Handling and preparation of the samples for analysis, as well as shipping and storage requirements, will be provided in a separate study manual.

Measurement of bAb and nAb levels will be performed in a laboratory designated by the Sponsor.

According to the ICF (Section 10.2.6), serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoVs.

The maximum planned volume of blood sampled per participant for immunogenicity assessments in 1 day is 21 mL.

7.3. Efficacy Assessments

7.3.1. Vaccine Effectiveness Assessments

Vaccine effectiveness for adolescents of ages of 12 to < 18 years will be inferred based on serum Ab responses obtained on Day 57 (28 days after the second injection of mRNA-1273). Inference will be based on assessing the adolescent Ab responses against the following:

1. *If available at the time of analysis*, adolescent Ab responses will be assessed against an accepted serum nAb threshold conferring protection against COVID-19.
2. *If an accepted threshold of protection is not available*, adolescent Ab responses will be assessed by establishing noninferiority of the GM value of serum nAb from adolescent participants compared with the GM value of serum nAb from adults enrolled in the ongoing clinical endpoint efficacy trial (Study P301). The statistical parameters to infer effectiveness are described in Section 2.

Each study participant will have an NP swab sample collected for SARS-CoV-2 testing by RT-PCR on Day 1, prior to receiving a dose of the IP as specified in SoA (Table 6).

COVID-19:

To be considered as a case of COVID-19 for the evaluation of the primary efficacy endpoint, the following case definition must be met:

- The participant must have experienced at least TWO of the following systemic symptoms: Fever (≥ 38ºC/≥ 100.4ºF), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
- The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
- The participant must have at least 1 NP swab or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.

Severe COVID-19:

To be considered severe COVID-19, the following criteria must be met:

- Confirmed COVID-19 as per the primary efficacy endpoint case definition, plus any of the following:
  - Clinical signs indicative of severe systemic illness, respiratory rates ≥ 30 per minute, heart rate ≥ 125 beats per minute, SpO2 ≤ 93% on room air at sea level or PaO2/FIO2 < 300 mm Hg, OR
  - Respiratory failure or Acute Respiratory Distress Syndrome (ARDS), (defined as needing high-flow oxygen, noninvasive or mechanical ventilation, or extracorporeal membrane oxygenation [ECMO]), evidence of shock (systolic blood pressure < 90 mmHg, diastolic BP < 60 mmHg or requiring vasopressors), OR
  - Significant acute renal, hepatic, or neurologic dysfunction, OR
  - Admission to an ICU or death.

The secondary case definition of COVID-19 is defined as the following systemic symptoms: fever (temperature > 38ºC/≥ 100.4ºF), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea AND a positive NP swab or saliva sample for SARS-CoV-2 by RT-PCR.

Death attributed to COVID-19 is defined as any participant who dies during the study with a cause directly attributed to a complication of COVID-19.

SARS-CoV-2 Infection:

- SARS-CoV-2 infection is defined by seroconversion measured by bAb against SARS-CoV-2 nucleocapsid protein. Seroconversion is defined differently for participants seronegative at Baseline and seropositive at Baseline:
  - Participants seronegative at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein either from below the limit of detection (LOD) or lower limit of quantification (LLOQ) at Day 1 which increase to equal to or above LOD or LLOQ starting at Day 57 or later.
  - Participants seropositive at Baseline: bAb levels against SARS-CoV-2 nucleocapsid protein above the LOD or LLOQ at Day 1 that increase by 4-fold or more in participants with pre-existing bAb starting at Day 57 or later.

7.3.2. Surveillance for COVID-19 Symptoms:

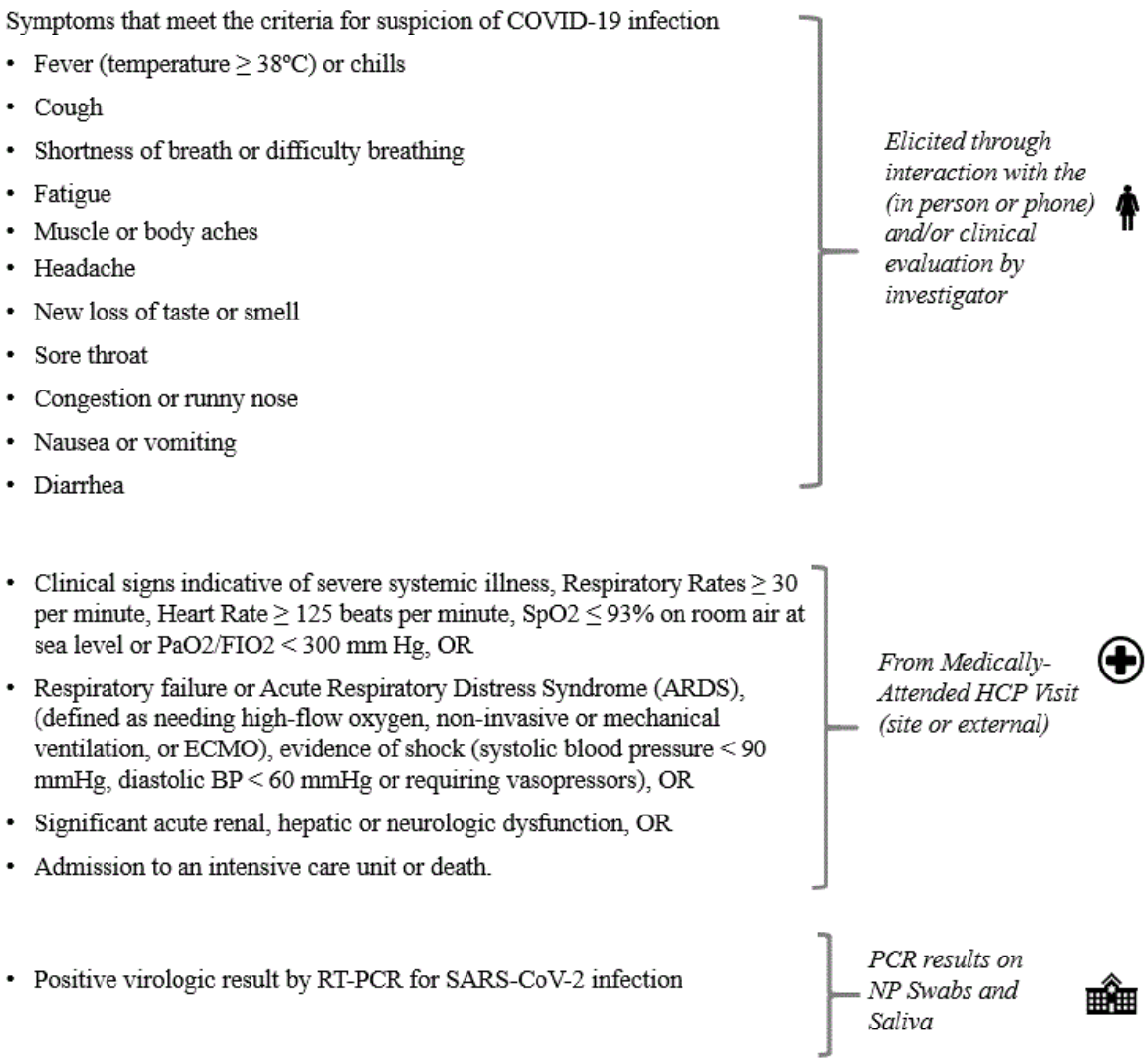
Surveillance for COVID-19 symptoms will be conducted via biweekly telephone calls or eDiary prompts as specified in Section 7.1.1 and Figure 2; starting after participant enrollment and throughout the study.

If there is no response to an eDiary prompt for 2 days, the study site staff will contact the study participant by phone.

According to the CDC as of 10 Jun 2020 (CDC 2020c), patients with COVID-19 have reported a wide range of symptoms ranging from mild symptoms to severe illness. Throughout the study, to survey for COVID-19, the following prespecified symptoms that meet the criteria for suspicion of COVID-19 will be elicited weekly from the participant and the presence of any one of these symptoms lasting at least 48 hours (except for fever and/or respiratory symptoms) will result in the study site staff arranging an illness visit to collect an NP swab within 72 hours:

- Fever (temperature ≥ 38ºC/≥ 100.4ºF) or chills (of any duration, including ≤ 48 hours)
- Shortness of breath or difficulty breathing (of any duration, including ≤ 48 hours)
- Cough (of any duration, including ≤ 48 hours)
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhea

Figure 2: Surveillance for COVID-19 Symptoms and the Corresponding Clinical Data Pathways



Abbreviations: BP = blood pressure, COVID-19 = coronavirus disease 2019, ECMO, SpO2 = oxygen saturation, PaO2 = partial pressure of oxygen, FIO2 = fraction of inspired oxygen, HCP = healthcare practitioner, RT-PCR = reverse transcriptase polymerase chain reaction, SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

It is important to note that some of the symptoms of COVID-19 overlap with solicited systemic ARs that are expected after vaccination with mRNA-1273 (eg, myalgia, headache, fever, and chills). During the first 7 days after vaccination, when these solicited ARs are common, investigators should use their clinical judgement to decide if an NP swab should be collected. The collection of an NP swab prior to the Day 1 and Day 29 vaccination can help ensure that cases of COVID-19 are not overlooked. Any study participant who reports respiratory symptoms during the 7-day period after vaccination should be evaluated for COVID-19.

During the course of the study, participants with symptoms of COVID-19 will be asked to return within 72 hours or as soon as possible to the study site or medically qualified staff from the study site will conduct a home visit as soon as possible to collect an NP swab sample (for RT-PCR) for evaluation of COVID-19. Both study site visits and home visits are referred to as illness visits (Section 7.1.6). The NP swab sample will also be tested for the presence of other respiratory infections. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis (Section 7.3.3). At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection. In addition, the study site may collect an additional respiratory sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care.

Cases are defined as participants meeting clinical criteria based both on symptoms for COVID-19 and on RT-PCR detection of SARS-CoV-2 from samples collected within 72 hours of the study participant reporting symptoms meeting the definition of COVID-19. Participants who are hospitalized for COVID-19 without the opportunity for a clinic or home visit will also be considered cases, assuming that the symptomology criteria for COVID-19 are met and a respiratory sample is positive for SARS-CoV-2 by PCR at a clinical laboratory improvement amendments (CLIA)-certified laboratory. Investigators are encouraged to try to obtain a respiratory sample during the course of hospitalization for submission to the study central laboratory, if feasible. The investigator should determine if the criteria for severe COVID-19 has been met.

Severe COVID-19 is defined in Section 7.3.1.

All clinical findings will be recorded in the eCRF. All confirmed cases of COVID-19 will be captured as MAAEs, along with relevant concomitant medications and details about severity, seriousness, and outcome, and will be reported immediately to the Sponsor or designee (Section 7.4.4).

7.3.3. Follow up/Convalescent Period After Diagnosis with COVID-19

Any confirmed COVID-19 occurring in a participant will be captured as an MAAE along with relevant concomitant medications and details about severity, seriousness, and outcome. Study participants will be monitored by medically qualified study site personnel for a 28-day period after diagnosis. Additionally, a convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection (Table 6). The investigator should determine if the criteria for severe COVID-19 has been met. If the participant is hospitalized, medically qualified study site personnel will try to obtain medical records and SARS-CoV-2 diagnostic results. If the participant is later discharged from the hospital during the

28-day period following diagnosis of COVID-19, the study site personnel will arrange for a resumption of the protocol schedule.

7.4. Safety Definitions and Related Procedures

7.4.1. Adverse Event

An AE is defined as any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Events Meeting the Adverse Event Definition

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition
- New conditions detected or diagnosed after the first dose of IP even though they may have been present before the start of the study

Events NOT Meeting the Adverse Event Definition

- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure should be the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).

An AR is any AE for which there is a reasonable possibility that the vaccine caused the AE (Section 7.4.9). For the purposes of investigational new drug safety reporting, "reasonable possibility" means that there is evidence to suggest a causal relationship between the vaccine and the AE.

An unsolicited AE is any AE reported by the participant that is not specified as a solicited AR in the protocol or is specified as a solicited AR but starts outside the protocol-defined period for reporting solicited ARs (ie, for the 7 days after each dose of vaccine).

7.4.2. Serious Adverse Events

An AE (including an AR) is considered an SAE if, in the view of either the investigator or Sponsor, it results in any of the following outcomes:

- **Death**
  A death that occurs during the study or that comes to the attention of the investigator during the protocol-defined follow-up period must be reported to the Sponsor, whether or not it is considered related to the IP.

- **Is life-threatening**
  An AE is considered life-threatening if, in the view of either the investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.
- **Inpatient hospitalization or prolongation of existing hospitalization**
  In general, inpatient hospitalization indicates the participant was admitted to the hospital or emergency ward for at least one overnight stay for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. The hospital or emergency ward admission should be considered an SAE regardless of whether opinions differ as to the necessity of the admission. Complications that occur during inpatient hospitalization will be recorded as an AE; however, if a complication/AE prolongs hospitalization or otherwise fulfills SAE criteria, the complication/AE will be recorded as a separate SAE.
- **Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions**
  This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea/vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
- **Congenital anomaly or birth defect**
- **Medically important event**
  Medical judgment should be exercised in deciding whether SAE reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

7.4.3. Solicited Adverse Reactions

The term "reactogenicity" refers to the occurrence and intensity of selected signs and symptoms (ARs) occurring after IP injection. The eDiary will solicit daily participant reporting of ARs using a structured checklist (Section 7.1.1). Participants will record such occurrences in an eDiary on the day of each dose injection and for the 6 days after the day of dosing.

Severity grading of reactogenicity will occur automatically based on participant entry into the eDiary according to the grading scales presented in Table 3 modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until it resolves or the next IP injection occurs whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in the eDiary beyond Day 7 should be reviewed by the study site staff either during the next scheduled telephone call or at the next study site visit. All solicited ARs (local and systemic) will be considered causally related to dosing.

Table 3: Solicited Adverse Reactions and Grades

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[a]
Injection site pain	None	Does not interfere with activity	Repeated use of over-the-counter pain reliever > 24 hours or interferes with activity	Any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Injection site erythema (redness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis or exfoliative dermatitis
Injection site swelling/induration (hardness)	< 25 mm/ < 2.5 cm	25 - 50 mm/ 2.5 - 5 cm	51 - 100 mm/ 5.1 - 10 cm	> 100 mm/ > 10 cm	Necrosis
Axillary (underarm) swelling or tenderness ipsilateral to the side of injection	None	No interference with activity	Repeated use of over-the-counter (non-narcotic) pain reliever > 24 hours or some interference with activity	Any use of prescription (narcotic) pain reliever or prevents daily activity	Emergency room visit or hospitalization
Headache	None	No interference with activity	Repeated use of over-the-counter pain reliever > 24 hours or some interference with activity	Significant; any use of prescription pain reliever or prevents daily activity	Requires emergency room visit or hospitalization
Fatigue	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Myalgia (muscle aches all over body)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Arthralgia (joint aches in several joints)	None	No interference with activity	Some interference with activity	Significant; prevents daily activity	Requires emergency room visit or hospitalization
Nausea/vomiting	None	No interference with activity or 1-2 episodes/ 24 hours	Some interference with activity or > 2 episodes/24 hours	Prevents daily activity, requires outpatient intravenous hydration	Requires emergency room visit or hospitalization for hypotensive shock

Reaction	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4[a]
Chills	None	No interference with activity	Some interference with activity not requiring medical intervention	Prevents daily activity and requires medical intervention	Requires emergency room visit or hospitalization
Fever (oral)	< 38.0°C < 100.4°F	38.0 – 38.4°C 100.4 - 101.1°F	38.5 – 38.9°C 101.2 – 102.0°F	39.0 – 40.0°C 102.1 - 104.0°F	> 40.0°C > 104.0°F

a. Grading for Grade 4 events per investigator assessment (with exception of fever).

Source: Guidance for industry - Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007).

Any solicited AR that meets any of the following criteria must be entered into the participant's source document and must also be recorded by the study site staff on the solicited AR page of the participant's eCRF:

- Solicited local or systemic AR that results in a visit to a healthcare practitioner (HCP; otherwise meets the definition of an MAAE)
- Solicited local or systemic AR leading to the participant withdrawing from the study or the participant being withdrawn from the study by the investigator (AE leading to withdrawal)
- Solicited local or systemic AR lasting beyond 7 days after injection
- Solicited local or systemic AR that leads to participant withdrawal from IP
- Solicited local or systemic AR that otherwise meets the definition of an SAE

7.4.4. Medically Attended Adverse Events

An MAAE is an AE that leads to an unscheduled visit to an HCP. This would include visits to a study site for unscheduled assessments (eg, abnormal laboratory test results follow-up, COVID-19 [Section 7.3.1) and visits to HCPs external to the study site (eg, urgent care, primary care physician). Investigators will review unsolicited AEs for the occurrence of any MAAE. All MAAEs must be fully reported on the MAAE page of the eCRF.

All confirmed COVID-19 cases (Section 7.3.1) will be recorded as MAAEs and reported to the Sponsor or designee immediately and in all circumstances within 24 hours, using the SAE Mailbox, the SAE Hotline, or the SAE Fax line (Section 7.4.11). The investigator will submit any updated COVID-19 case data to the Sponsor within 24 hours of it being available.

7.4.5. Adverse Events of Special Interest

Any AESIs of MIS-C will be collected through the entire study period.

Investigators will be asked to report, as AESI, clinical signs/symptoms consistent with the CDC case definition of MIS-C (https://emergency.cdc.gov/han/2020/han00432.asp):

- An individual aged < 21 years presenting with fever, laboratory evidence of inflammation, and evidence of clinically severe illness requiring hospitalization, with multisystem (> 2) organ involvement (cardiac, renal, respiratory, hematologic, gastrointestinal, dermatologic or neurological);

AND

- No alternative plausible diagnoses;

AND

- Positive for current or recent SARS-CoV-2 infection by RT-PCR, serology, or antigen test; or COVID-19 exposure within the 4 weeks prior to the onset of symptoms:

    1. Fever ≥ 38.0°C/≥ 100.4ºF for ≥ 24 hours, or report of subjective fever lasting ≥ 24 hours
    2. Including, but not limited to, one or more of the following: an elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, procalcitonin, d-dimer, ferritin, lactic acid dehydrogenase (LDH), or interleukin 6 (IL-6), elevated neutrophils, reduced lymphocytes, and low albumin

Some individuals may fulfill full or partial criteria for Kawasaki disease but should be reported if they meet the case definition for MIS-C. Consider MIS-C in any pediatric death with evidence of SARS-CoV-2 infection.

7.4.6. Recording and Follow-up of Pregnancy

Female individuals who have a positive pregnancy test at Screening should not be enrolled; participants who have a positive pregnancy test any time during the study should receive no further dosing with IP but should be asked to remain in the study and be monitored for safety.

Details of all pregnancies in female participants will be collected after the start of study treatment and until the end of their participation in the study.

- If a pregnancy is reported, the investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in this section.
- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

Pregnancies occurring in participants after enrollment must be reported to Sponsor or designee within 24 hours of the study site learning of its occurrence, using the SAE Mailbox, the SAE

Hotline, or the SAE Fax line (Section 7.4.11). If the participant agrees to submit this information, the pregnancy must be followed to determine the outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if intended duration of the safety follow-up for the study has ended. Pregnancy report forms will be distributed to the study site to be used for this purpose. The investigator must immediately (within 24 hours of awareness) report to the Sponsor any pregnancy resulting in an abnormal outcome according to the procedures described for SAEs.

7.4.7. Eliciting and Documenting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the eCRF and reported to the Sponsor.

Solicited ARs will be collected from Day 1 through 7 days after each dose. Other (unsolicited) AEs will be collected from Day 1 through 28 days after each dose.

Both MAAEs and SAEs will be collected from participants as specified in the SoA until the end of their participation in the study. Any AEs that occur before administration of IP will be analyzed separately from AEs.

At every study site visit or telephone contact, participants will be asked a standard question to elicit any medically related changes in their well-being (including COVID-19 symptoms) according to the scripts provided. Participants will also be asked if they have been hospitalized, had any accidents, used any new medications, changed concomitant medication regimens (both prescription and over-the-counter medications), or had any nonstudy vaccinations.

In addition to participant observations, physical examination findings, or data relevant to participant safety classified as an AE will be documented on the AE page of the eCRF.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU (as defined in Section 6.4).

7.4.8. Assessment of Intensity

An event is defined as “serious” when it meets at least one of the predefined outcomes as described in the definition of an SAE (Section 7.4.2), NOT when it is rated as severe.

The severity (or intensity) of an AR or AE refers to the extent to which it affects the participant’s daily activities. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) will be used to categorize local and systemic

reactogenicity events (solicited ARs), and vital sign measurements observed during this study. Specific criteria for local and systemic reactogenicity events are presented in Section 7.4.3.

The determination of severity for all unsolicited AEs should be made by the investigator based upon medical judgment and the definitions of severity as follows:

- Mild: These events do not interfere with the participant's daily activities.
- Moderate: These events cause some interference with the participant's daily activities and require limited or no medical intervention.
- Severe: These events prevent the participant's daily activity and require intensive therapeutic intervention.

Study staff should elicit from the participant the impact of AEs on the participant's activities of daily living to assess severity and document appropriately in the participant's source documentation. Changes in the severity of an AE should be documented in the participant's source documentation to allow an assessment of the duration of the event at each level of intensity to be performed. An AE characterized as intermittent requires documentation of onset and duration of each episode. An AE that fluctuates in severity during the course of the event is reported once in the eCRF at the highest severity observed.

7.4.9. Assessment of Causality

The investigator's assessment of an AE's relationship to IP is part of the documentation process but is not a factor in determining what is or is not reported in the study.

The investigator will assess causality (ie, whether there is a reasonable possibility that the IP caused the event) for all AEs and SAEs. The relationship will be characterized using the following classification:

Not related: There is not a reasonable possibility of a relationship to the IP. Participant did not receive the IP OR temporal sequence of the AE onset relative to administration of the IP is not reasonable OR the AE is more likely explained by another cause than the IP.

Related: There is a reasonable possibility of a relationship to the IP. There is evidence of exposure to the IP. The temporal sequence of the AE onset relative to the administration of the IP is reasonable. The AE is more likely explained by the IP than by another cause.

7.4.10. Reporting Adverse Events

The investigator is responsible for reporting all AEs that are observed or reported during the study, regardless of their relationship to IP or their clinical significance. If there is any doubt as to whether a clinical observation is an AE, the event should be reported.

All unsolicited AEs reported or observed during the study will be recorded on the AE page of the eCRF. Information to be collected includes the type of event, time of onset, investigator-specified assessment of severity (impact on activities of daily living) and relationship to IP, time of resolution of the event, seriousness, as well as any required treatment or evaluations, and outcome. The unsolicited AEs resulting from concurrent illnesses, reactions to concurrent illnesses, reactions to concurrent medications, or progression of disease states must also be reported. All AEs will be followed until they are resolved or stable or judged by the investigator to be not clinically significant. The Medical Dictionary for Regulatory Activities (MedDRA) will be used to code all unsolicited AEs.

Any medical condition that is present at the time that the participant is screened but does not deteriorate should not be reported as an unsolicited AE. However, if it deteriorates at any time during the study, it should be recorded as an unsolicited AE.

7.4.11. Reporting SAEs

Prompt notification by the investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

Any AE considered serious by the investigator or that meets SAE criteria (Section 7.4.2) must be reported to the Sponsor immediately (within 24 hours of becoming aware of the SAE). The investigator will assess whether there is a reasonable possibility that the IP caused the SAE. The Sponsor will be responsible for notifying the relevant regulatory authorities of any SAE as outlined in the 21 US CFR Parts 312 and 320. The investigator is responsible for notifying the institutional review board (IRB) directly.

If the eCRF is unavailable at the time of the SAE, the following contact information is to be used for SAE reporting:

- SAE Mailbox: Safety_Moderna@iqvia.com
- SAE Hotline (USA and Canada): +1-866-599-1341
- SAE Fax line (USA and Canada): +1-866-599-1342

Regulatory reporting requirements for SAE are described in Section 7.4.15.

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE, including SAEs, and remain responsible for following up AEs that are serious, considered related to IP or study procedures, or that caused the participant to discontinue the study.

7.4.12. Time Period and Frequency for Collecting AE and SAE Information

Medical occurrences that begin before the start of IP dosing but after obtaining informed consent will be recorded in the Medical History/Current Medical Conditions section of the eCRF and not in the AE section; however, if the condition worsens at any time during the study, it will be recorded and reported as an AE.

Adverse events may be collected as follows:

- Observing the participant
- Receiving an unsolicited complaint from the participant
- Questioning the participant in an unbiased and nonleading manner

Solicited ARs will be collected from the day of injection through 6 days after each dose. Other (unsolicited) AEs will be collected from the day of injection through 28 days after each dose.

SAEs will be collected from the start of IP dosing until the last day of study participation.

All SAEs will be recorded and reported to the Sponsor or designee immediately and in all circumstances within 24 hours. The investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

An abnormal value or result from a clinical or laboratory evaluation can also indicate an AE if it is determined by the investigator to be clinically significant (eg, leads to dose modification or study drug discontinuation, or meets any serious criteria). If this is the case, it must be recorded in the source document and as an AE on the appropriate AE form(s). The evaluation that produced the value or result should be repeated until that value or result returns to normal or is stabilized and the participant's safety is not at risk.

Investigators are not obligated to actively seek AEs or SAEs after EOS participation. However, if the investigator learns of any SAE (including a death) at any time after a participant has withdrawn from or completed the study, and the investigator considers the event to be reasonably related to the IP or study participation, the investigator must promptly notify the Sponsor.

7.4.13. Method of Detecting AEs and SAEs

Electronic diaries have specifically been designed for this study by the Sponsor. The diaries will include prelisted AEs (solicited ARs) and intensity scales; they will also include blank space for the recording of information on other AEs (unsolicited AEs) and concomitant medications/vaccinations.

The investigator is responsible for the documentation of AEs regardless of treatment group or suspected causal relationship to IP. For all AEs, the investigator must pursue and obtain information adequate to determine the outcome of the AE and to assess whether the AE meets the

criteria for classification as an SAE requiring immediate notification to the Sponsor or its designated representative.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about the occurrence of AE.

7.4.14. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits and contacts.

All AEs and SAEs will be treated as medically appropriate and followed until resolution, stabilization, the event is otherwise explained, or the participant is LTFU, as defined in Section 6.4.

7.4.15. Regulatory Reporting Requirements for SAEs

- Prompt notification by the investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs, and investigators.
- Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and Sponsor policy and forwarded to investigators as necessary.
- An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

7.5. Safety Monitoring

The CRO's medical monitor, the Sponsor's medical monitor, and the individual study site investigators will monitor safety throughout the study.

7.5.1. Data Safety Monitoring Board

Safety oversight will be under the direction of a DSMB composed of external independent consultants with relevant expertise. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will have separate meetings by teleconference to review unblinded safety data when half of the study population (1,500 randomized participants)

have reached Day 8 (1 week after dose 1) and again approximately when 25% (750), 50% (1,500), and 75% (2,250) of enrolled participants have reached Day 36 (1 week after dose 2). Recruitment will continue, as applicable, during the DSMB review period. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. Details regarding the DSMB composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

The DSMB will convene on an ad hoc basis if any of the pause rules, described in Section 6.4, are met. The DSMB will review all available unblinded study data to adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

7.6. Treatment of Overdose

As the study treatment is to be administered by a healthcare professional, it is unlikely that an overdose will occur. Dose deviations will be tracked as protocol deviations (Section 10.2.8).

7.7. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

7.8. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

7.9. Biomarkers

Immunogenicity assessments are presented in Section 7.2. Biomarkers are not evaluated in this study.

7.10. Health Economics

Health economics are not evaluated in this study.

8. STATISTICAL ANALYSIS PLAN

This section summarizes the planned statistical analysis strategy and procedures for the study. The details of statistical analysis will be provided in the statistical analysis plan (SAP), which will be finalized before the clinical database lock for the study. If changes are made to primary and/or key secondary objectives and hypotheses or the statistical methods related to those hypotheses after the study has begun but prior to any data unblinding, then the protocol will be amended (consistent with ICH Guideline E9). Changes to other secondary or exploratory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the SAP or clinical study report (CSR) for the study. Ad hoc exploratory analyses, if any, will be clearly identified in the CSR.

8.1. Blinding and Responsibility for Analyses

This is an observer-blind study. The investigator, study staff, study participants, study site monitors, and Sponsor personnel (or its designees) will be blinded to the IP administered until study end, with the following exceptions:

- Unblinded pharmacy personnel (of limited number) will be assigned to vaccine accountability procedures and will prepare and administer mRNA-1273 (or placebo) to all participants. These pharmacy personnel will have no study functions other than study vaccine management, documentation, accountability, preparation, and administration. They will not be involved in participant evaluations and will not reveal the identity of IP to either the participant or the blinded study site personnel involved in the conduct of the study unless this information is necessary in the case of an emergency.
- Unblinded study site monitors, not involved in other aspects of monitoring, will be assigned as the IP accountability monitors. They will have responsibilities to ensure that study sites are following all proper IP accountability, preparation, and administration procedures.
- An unblinded statistical and programming team will perform the preplanned interim analyses (IAs, Section 8.6.1). Sponsor team members will be prespecified to be unblinded to the IA results and will not communicate the results of IA to the blinded investigators, study site staff, clinical monitors, or participants.

The dosing assignment will be concealed by having the unblinded pharmacy personnel prepare the IP in a secure location that is not accessible or visible to other study staff. An opaque sleeve over the syringe used for injection will maintain the blind at the time of injection, as the doses containing mRNA-1273 will look different to that of placebo. Only delegated unblinded study site staff will conduct the injection procedure. Once the injection is completed, only the blinded study staff will

perform further assessments and interact with the participants. Access to the randomization code will be strictly controlled at the pharmacy.

The planned study analyses are described in Section 8.6.

8.1.1. Breaking the Blind

A participant or participants may be unblinded in the event of an SAE or other severe event, or if there is a medical emergency requiring the identity of the product to be known to properly treat a participant. If a participant becomes seriously ill or pregnant during the study, the blind will be broken if knowledge of the administered vaccine will affect that participant's dosing options. In the event of a medical emergency requiring identification of the vaccine administered to an individual participant, the investigator will make every attempt to contact the Sponsor medical lead to explain the need for opening the code within 24 hours of opening the code. The investigator will be responsible for documenting the time, date, reason for the code break, and the names of the personnel involved.

In addition to the aforementioned situations where the blind may be broken, the data will also be unblinded to a statistical team at specified time points for interim analyses as outlined in Section 8.6.1.

8.2. Statistical Hypothesis

If an accepted threshold based on SARS-CoV-2 S protein (S2P) is established for the primary immunogenicity objective, the null hypothesis is that the percentage of participants on mRNA-1273 with SARS-CoV-2 S2P serum Ab above the established threshold on Day 57 is $\leq 60\%$ (ie, H_0: percentage of participants on mRNA-1273 $\leq 60\%$ with SARS-CoV-2 S2P serum Ab on Day 57 above the established threshold).

The study would be considered to meet the immunogenicity objective if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 60% (lower bound of the 95% CI > 60%).

If an accepted serum Ab threshold of protection against COVID-19 is not available for the primary immunogenicity objective, the null hypothesis will be based on SARS-CoV-2 S2P serum nAb.

H_0: immunogenicity response to mRNA-1273 is inferior in adolescents (12 to < 18 years of age) compared with that in adults ($\geq$ 18 years of age) using mRNA-1273 Study P301 data, based on SARS-CoV-2 S2P serum nAb on Day 57.

The study would be considered to meet the primary immunogenicity objective if noninferiority in immune response in adolescents compared with that in adults is demonstrated by the lower bound of the 95% CI of the geometric mean ratio (GMR) rules out 0.5 (lower bound > 0.5) using a

noninferiority margin of 2. The GMR is the ratio of the GM value of adolescents on mRNA-1273 in this Study P203 compared with the GM value of adults on mRNA-1273 in Study P301 on Day 57.

8.3. Power and Sample Size

The sample size of this study is driven by safety. Approximately 3,000 participants will be randomly assigned in a 2:1 ratio to receive mRNA-1273 and placebo (Section 5.2). With 2,000 participants exposed to mRNA-1273, the study has at least 90% probability to observe at least 1 participant with an AE at a true 0.25% AE rate.

Serum samples from all participants will be collected and banked, a subset of participants will be selected, and their samples will be processed for immunogenicity testing (the Immunogenicity Subset).

Approximately 210 participants who receive mRNA-1273 will be selected for the Immunogenicity Subset, with a target of 178 participants in the PP Immunogenicity Subset (adjusting for approximately 15% of participants who may be excluded from the PP Immunogenicity Subset, as they may not have immunogenicity results due to any reason). The sample size of the Immunogenicity Subset may be updated with data from other mRNA-1273 studies or external data especially regarding a threshold of protection. In such a situation, the final sample size of the Immunogenicity Subset will be documented in the SAP.

For the primary immunogenicity objective, with approximately 178 participants, the study will have > 90% power to rule out 60% with a 2-sided 95% CI for the percentage of mRNA-1273 participants exceeding the acceptable threshold if the true rate of participants exceeding the acceptable threshold is 75%. With approximately 178 participants, there will be 90% power to demonstrate noninferiority of the immune response in adolescents at a 2-sided alpha of 0.05, compared with that in adults (in Study P301) receiving mRNA-1273, assuming an underlying GMR value of 1 and a noninferiority margin of 2. The standard deviation (SD) of the log-transformed levels is assumed to be 2.

8.4. Analysis Sets

The analysis sets are defined in Table 4.

Table 4: Analysis Sets

Analysis Set	Description
Randomization Set	All participants who are randomized, regardless of the participants' treatment status in the study.
Full Analysis Set (FAS)	All randomized participants who received at least 1 injection of IP.
Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing.
Per-protocol (PP) Immunogenicity Subset	A subset of participants in the FAS will be selected for immunogenicity testing. The PP Immunogenicity Subset includes participants selected for the Immunogenicity Subset who received planned doses of study vaccination per schedule, complied with immunogenicity testing schedule, and have no major protocol deviations that impact key or critical data. Participants who are seropositive at baseline will be excluded from the PP Immunogenicity Subset. The PP Immunogenicity Subset will be used for analyses of immunogenicity unless specified otherwise.
PP Set for Efficacy	All participants in the FAS who received planned doses of study vaccination, had no immunologic or virologic evidence of prior COVID-19, and have no major protocol deviations that impact key or critical efficacy data.
Solicited Safety Set	The Solicited Safety Set consists of FAS participants who contributed any solicited AR data. The Solicited Safety Set will be used for the analyses of solicited ARs.
Safety Set	All randomized participants who receive at least 1 dose of IP. The Safety Set will be used for all analyses of safety except for the solicited ARs.

Abbreviations: AR = adverse reaction; COVID 19 = coronavirus disease 2019; IP = investigational product.

8.5. Statistical Methods

8.5.1. Baseline Characteristics and Demographics

Demographic variables (eg, age, height, weight, and BMI) and baseline characteristics will be summarized by treatment group. Summary statistics (mean, SD for continuous variables, and number and percentage for categorical variables) will be provided.

8.5.2. Safety Analyses

All safety analyses will be based on the Safety Set, except summaries of solicited ARs, which will be based on the Solicited Safety Set. All safety analyses will be provided by treatment group.

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic events), unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to discontinuation, vital sign measurements, and physical examination findings.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each injection will be summarized.

The number and percentage of participants with any solicited local AR, with any solicited systemic AR, and with any solicited AR during the 7-day follow-up period after each dose will be provided. A 2-sided 95% exact CI using the Clopper-Pearson method will also be provided for the percentage of participants with any solicited AR.

The number and percentage of participants with unsolicited AEs, SAEs, MAAEs, Grade 3 or higher ARs and AEs, and AEs leading to discontinuation from IP or withdrawal from the study will be summarized. Unsolicited AEs will be presented by MedDRA preferred term and system organ class.

The number of events of solicited ARs, unsolicited AEs/SAEs, and MAAEs will be reported in summary tables accordingly.

For all other safety parameters, descriptive summary statistics will be provided, and Table 5 summarizes analysis strategy for safety parameters. Further details will be described in the SAP.

Table 5: Analysis Strategy for Safety Parameters

Safety Endpoint	Number and Percentage of Participants, Number of Events	95% CI
Any solicited AR (overall and by local, systemic)	X	X
Any unsolicited AE	X	—
Any SAE	X	—
Any unsolicited MAAE	X	—
Any unsolicited treatment-related AE	X	—
Any treatment-related SAE	X	—
Discontinuation due to AE	X	—
Any severe AE	X	—
Any treatment-related severe AE	X	—

Abbreviations: AE = adverse event; AR = adverse reaction; CI = confidence interval; MAAE = medically attended adverse event; PT = preferred term; SAE = serious adverse event; SOC = system organ class.
Notes: 95% CI using the Clopper-Pearson method, X = results will be provided. Unsolicited AEs will be summarized by SOC and PT coded by MedDRA.

8.5.3. Immunogenicity Analyses

The SAP will describe the complete set of immunogenicity analyses, including the approach to sample participants into an Immunogenicity Subset for analysis of immunogenicity. The PP Immunogenicity Subset is the primary analysis set for immunogenicity unless otherwise specified. The primary immunogenicity objective of this study is to use the immunogenicity response to infer efficacy in adolescents (12 to < 18 years in this study).

If an accepted serum Ab threshold of protection against COVID-19 is available based on data from other mRNA-1273 studies or external data, the number and percentage of participants with Ab greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. If the lower bound of the 95% CI on the mRNA-1273 group is > 60%, the primary immunogenicity objective of this study will be considered to be met.

The percentage of participants with serum Ab greater than or equal to the threshold with 95% CI will be provided by vaccination group (mRNA-1273 and placebo) at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

The GM level of serum Ab with corresponding 95% CI will be provided at each time point by vaccination group. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation.

In addition, an analysis of covariance (ANCOVA) model with vaccination group as explanatory variables, adjusting for baseline value if applicable, will be used to assess the effect of mRNA-1273 at postbaseline time points with Day 57 as the time point of primary interest. The geometric least squares mean (GLSM) with 95% CI for each vaccination group and GMR with

95% CI for difference between mRNA-1273 and placebo will be estimated from the ANCOVA model.

If an accepted serum Ab threshold of protection against COVID-19 is not established, the noninferiority of immune response in adolescents compared with that in adults will be assessed. Noninferiority of the immune response in adolescents in this study at a 2-sided alpha of 0.05, compared with that in adults in Study P301 receiving mRNA-1273, will be considered to be demonstrated if the lower bound of the 95% CI of GMR is > 0.5 using a noninferiority margin of 2.

For SARS-CoV-2 S2P-specific bAb, the number and percentage of participants with seroconversion due to vaccination, GM level for specific nAb and bAb, GMFR of nAb and bAb with corresponding 95% CI will be provided at each time point with Day 57 as the primary time points of interest.

8.5.4. Efficacy Analysis

To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo, the incidence rate will be provided by vaccination group, calculated as the number of cases divided by the total person-time. The incidence rate ratio of mRNA-1273 versus placebo will be provided with its 95% CI computed using the exact method conditional upon the total number of cases adjusted by the total person-time.

For serologically-confirmed SARS-CoV-2 infection or COVID-19, regardless of symptomatology or severity, infection rate will be provided by vaccination group and the infection rate ratio of mRNA-1273 versus placebo with its 95% CI using the exact method conditional upon the total number of cases adjusted by the total person-time.

8.5.5. Exploratory Analyses

Exploratory analyses will be described in the SAP before database lock.

8.5.6. Subgroup Analyses

Subgroup analyses will be performed as described in the SAP.

8.6. Study Analyses

8.6.1. Interim Analyses

An interim analysis of safety and immunogenicity data is planned following Day 57 (1 month after dose 2). At the Sponsor’s discretion, a CSR may be developed for the interim analysis.

8.6.2. Final Analysis

The final analysis of all endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in a final CSR, including individual listings.

Additional information about all study analyses may be provided in the SAP.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. APPENDIX 1: Schedule of Assessments

The schedule of assessments is presented in Table 6.

If a participant cannot attend a study site visit (scheduled or unscheduled) with the exception of Screening or Day 1, a home visit is acceptable if performed by appropriately delegated study site staff or a home healthcare service provided by the Sponsor (Section 7). If neither a participant visit to the study site nor a home visit to the participant is possible (with the aforementioned exceptions), a safety telephone call should be performed that includes the assessments scheduled for the safety telephone calls.

Table 6: Schedule of Assessments

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	± 2	± 3	± 14	± 2	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Informed consent/assent form, demographics, concomitant medications, medical history	X											
Review of inclusion and exclusion criteria	X	X										
Physical examination including vital signs, height, weight[6]	X	X		X		X			X			X
Pregnancy test[7]	X	X		X								
Randomization		X										
Study injection (including 60-minute postdose observation period)		X		X								
Blood sample for vaccine immunogenicity[8]		X				X			X			X
Nasopharyngeal swab sample for SARS-CoV-2[9]		X		X		X						

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	± 2	± 3	± 14	± 2	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Surveillance for COVID-19/ Illness visit[10]/ Unscheduled visit		X	X	X	X	X	X	X	X	X	X	X
Convalescent Visit[11]		X	X	X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[12]		X		X								
Review of eDiary data			X		X							
Follow-up safety telephone calls[13]								X		X		
Recording of unsolicited AEs		X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[14]		X	X	X	X	X	X		X	X		X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[14]		X	X	X	X	X	X		X	X		X
Recording of AESI (MIS-C)		X	X	X	X	X	X		X	X		X

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209[2, 3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[2, 3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	± 2	± 3	± 14	± 2	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Recording of concomitant medications and non-study vaccinations[14]		X	X	X	X	X						
Study completion												X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; FDA = US Food and Drug Administration; ICF = informed consent form; IRB = institutional review board; M = month; MAAE = medically attended AE; MIS-C = multisystem inflammatory syndrome of children; SC = safety (telephone) call; SFU = safety follow-up; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (DHHS 2020), investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor.

1. Day 0 and Day 1 may be combined on the same day. Additionally, the Day 0 visit may be performed over multiple visits if preformed within the 28-day screening window.
2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for “stay at home” or “shelter in place”), a safety telephone call to the participant should be made in place of the study site visit. The safety telephone call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Home visits will be permitted for all nondosing visits, with the exception of Screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Home visits must be permitted by the study site IRB and the participant via informed consent/assent and have prior approval from the Sponsor (or its designee).
3. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 +7 days as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for “stay at home” or “shelter in place”), the visit window may be extended to Day 29 + 21 days. When the extended visit window is used, the remaining study visits should be rescheduled to follow the inter-visit interval from the actual date of the second dose.
4. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363.
5. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.

6. Physical examination: A full physical examination, including height and weight, will be performed at Day 1, Day 29, Day 57, Day 209, and Day 394. BMI will be calculated only at Screening Visit (Day 0). Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE. Vital signs are to be measured pre- and post dose on days of injection (Day 1 and Day 29). When applicable, vital signs should be measured before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on Day 1 or Day 29 must have the visit rescheduled within the relevant visit window to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
7. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time.
8. Sample must be collected prior to dosing of injection on Day 1.
9. The nasopharyngeal swab sample will be used to ascertain the presence of SARS-CoV-2 via RT-PCR.
10. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for Covid-19, or new or ongoing AEs. If a participant meets the prespecified criteria of suspicion for COVID-19 (Section 7.1.6), the participants will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit, to include an NP swab sample (for RT-PCR testing) and other clinical evaluations. If a study site visit is not possible, a home visit may be arranged to collect the NP sample and conduct clinical evaluations. If a home visit is not possible, the participant will be asked to submit a saliva sample to the study site by a Sponsor-approved method. At this illness visit, the NP swab samples will be collected to evaluate for the presence of SARS-CoV-2 infection. NP swab samples will also be tested for the presence of other respiratory pathogens. In addition, the study site may collect an additional NP sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
11. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will be collected for potential immunologic assessment of SARS-CoV-2 infection
12. Diary entries will be recorded by the participant at approximately 1 hour after injection while at the study site with instruction provided by study staff. Study participants will continue to record entries in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolves or the next IP injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via telephone call or at the following study visit.
13. Trained study site personnel will call all participants to collect information relating to any AEs, MAAEs, SAEs, AEs leading to study withdrawal, information on concomitant medications associated with those events, and any nonstudy vaccinations. In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms.
14. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).

10.2. APPENDIX 2: Study Governance Considerations

10.2.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines.
- Applicable ICH GCP Guidelines.
- Applicable laws and regulatory requirements.
- The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- Any amendments to the protocol will require IRB approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:

– Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB

– Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures

– Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.2.2. Study Monitoring

Before an investigational site can enter a participant into the study, a representative of the Sponsor or its representatives will visit the investigational study site to do the following:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities with regard to protocol adherence, and the responsibilities of the Sponsor or its representatives. This will be documented in a clinical study agreement between the Sponsor, the designated CRO, and the investigator.

According to ICH GCP guidelines, the Sponsor of the study is responsible for ensuring the proper conduct of the study with regard to protocol adherence and validity of data recorded on the eCRFs. The study monitor's duties are to aid the investigator and the Sponsor in the maintenance of complete, accurate, legible, well-organized, and easily retrievable data. The study monitor will advise the investigator of the regulatory necessity for study-related monitoring, audits, IRB review, and inspection by providing direct access to the source data/documents. In addition, the study monitor will explain to and interpret for the investigator all regulations applicable to the clinical evaluation of an IP as documented in ICH guidelines.

It is the study monitor's responsibility to inspect the eCRFs and source documentation throughout the study to protect the rights of the participants; to verify adherence to the protocol; to verify completeness, accuracy, and consistency of the data; and to confirm adherence of study conduct to any local regulations. Details will be outlined in the Clinical Monitoring Plan. During the study, a monitor from the Sponsor or a representative will have regular contacts with the investigational site, for the following:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that the data are being accurately recorded in the eCRFs, and that IP accountability checks are being performed.
- Perform source data verification. This includes a comparison of the data in the eCRFs with the participant's medical records at the hospital or practice, and other records relevant to the study. This will require direct access to all original records for each participant (eg, clinical charts or electronic medical record system).
- Record and report any protocol deviations not previously sent.
- Confirm AEs and SAEs have been properly documented on eCRFs and confirm any SAEs have been forwarded to the SAE Hotline, and those SAEs that met criteria for reporting have been forwarded to the IRB.

The monitor will be available between visits if the investigator(s) or other staff needs information or advice.

10.2.3. Audits and Inspections

The Sponsor, their designee(s), the IRB, or regulatory authorities will be allowed to conduct study site visits to the investigational facilities for the purpose of monitoring or inspecting any aspect of the study. The investigator agrees to allow the Sponsor, their designee(s), the IRB, or regulatory

authorities to inspect the IP storage area, IP stocks, IP records, participant charts and study source documents, and other records relative to study conduct.

Authorized representatives of the Sponsor, a regulatory authority, and any IRB may visit the study site to perform audits or inspections, including source data verification. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, ICH E6(R2) GCP, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

The principal investigator must obtain IRB approval for the investigation. Initial IRB approval, and all materials approved by the IRB for this study including the participant consent/assent form and recruitment materials, must be maintained by the investigator and made available for inspection.

10.2.4. Financial Disclosure

The investigator is required to provide financial disclosure information to allow the Sponsor to submit the complete and accurate certification or disclosure statements required under 21 CFR 54. In addition, the investigator must provide the Sponsor with a commitment to promptly update this information if any relevant changes occur during the course of the investigation and for 1 year following the completion of the study.

The Sponsor, the CRO, and the study site are not financially responsible for further testing or treatment of any medical condition that may be detected during the screening process. In addition, in the absence of specific arrangements, the Sponsor, the CRO, and the study site are not financially responsible for further treatment of the disease under study.

10.2.5. Recruitment Procedures

Advertisements to be used for the recruitment of study participants, and any other written information regarding this study to be provided to the participant should be submitted to the Sponsor for approval. All documents must be approved by the IRB.

10.2.6. Informed Consent/Assent Process

The informed consent/assent document(s) must meet the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA), where applicable, and the IRB or study site. All consent documents will be approved by the appropriate IRB. The actual ICF used at each study site may differ, depending on local regulations and IRB requirements. However, all versions of the ICF must contain the standard information found in the

sample ICF provided by the Sponsor. Any change to the content of the ICF must be approved by the Sponsor and the IRB prior to the ICF being used.

If new information becomes available that may be relevant to the participant's willingness to continue participation in the study, this will be communicated to them in a timely manner. Such information will be provided via a revised ICF or an addendum to the original ICF.

The investigator or his/her representative will explain the nature of the study to the participant and answer all questions regarding the study.

The investigator is responsible for ensuring that the participant fully understands the nature and purpose of the study. Information should be given in both oral and written form whenever possible.

No participant should be obliged to participate in the study. The participant must be informed that participation is voluntary. Participants, their relatives, guardians, or (if applicable) LARs must be given ample opportunity to inquire about details of the study. The information must make clear that refusal to participate in the study or withdrawal from the study at any stage is without any prejudice to the participant's subsequent care.

The participant must be allowed sufficient time to decide whether they wish to participate in the study.

The participant must be made aware of, and give consent to, direct access to his/her source medical records by study monitors, auditors, the IRB, and regulatory authorities. The participant should be informed that such access will not violate participant confidentiality or any applicable regulations. The participant and/or participants' parent(s)/LAR(s) should also be informed that he/she is authorizing such access by signing the ICF.

A copy of the ICF(s) must be provided to the participant and/or participants' parent(s)/LAR(s).

A participant who is rescreened is not required to sign another ICF if the rescreening occurs within 28 days from the previous ICF signature date (within the initial Screening Period).

The ICF will also explain that excess serum from immunogenicity testing may be used for future research, which may be performed at the discretion of the Sponsor to further characterize the immune response to SARS-CoV-2, additional assay development, and the immune response across CoVs.

10.2.7. Protocol Amendments

No change or amendment to this protocol may be made by the investigator or the Sponsor after the protocol has been agreed to and signed by all parties unless such change(s) or amendment(s) has (have) been agreed upon by the investigator or the Sponsor. Any change agreed upon will be recorded in writing, and the written amendment will be signed by the investigator and the Sponsor.

IRB approval is required prior to the implementation of an amendment, unless overriding safety reasons warrant immediate action, in which case the IRB(s) will be promptly notified.

Any modifications to the protocol or the ICF, which may impact the conduct of the study, potential benefit of the study, or may affect participant safety, including changes of study objectives, study design, participant population, sample sizes, study procedures, or significant administrative aspects will require a formal amendment to the protocol. Such an amendment will be released by the Sponsor, agreed by the investigator(s), and approved by the relevant IRB(s) prior to implementation. A signed and dated statement that the protocol, any subsequent relevant amended documents, and the ICF have been approved by relevant IRB(s) must to be provided to the Sponsor before the study is initiated.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will be released by the Sponsor, agreed by the investigators, and notified to the IRB(s).

10.2.8. Protocol Deviations

The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of protocol deviations, corrective actions are to be developed by the study site and implemented promptly.

It is the responsibility of the study site investigator to use continuous vigilance to identify and report protocol deviations to the Sponsor or its designee. All protocol deviations must be addressed in study source documents, reported to study monitor. Protocol deviations must be sent to the reviewing IRB per their policies. The study site investigator is responsible for knowing and adhering to the reviewing IRB requirements.

10.2.9. Data Protection

Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by clinical quality assurance (QA) auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Individual participant medical information obtained as a result of this study is considered confidential, and disclosure to third parties is prohibited. Information will be accessible to authorized parties or personnel only. Medical information may be given to the participant's physician or to other appropriate medical personnel responsible for the participant's well-being. Each participant will be asked to complete a form allowing the investigator to notify the participant's primary health care provider of his/her participation in this study.

All laboratory specimens, evaluation forms, reports, and other records will be identified in a manner designed to maintain participant confidentiality. All records will be kept in a secure storage area with limited access. Clinical information will not be released without the written permission of the participant, except as necessary for monitoring and auditing by the Sponsor, its designee, relevant regulatory authority, or the IRB.

The investigator and all employees and coworkers involved with this study may not disclose or use for any purpose other than performance of the study, any data, record, or other unpublished, confidential information disclosed to those individuals for the purpose of the study. Prior written agreement from the Sponsor or its designee must be obtained for the disclosure of any confidential information to other parties.

10.2.10. Sample Retention and Future Biomedical Research

The retention period of laboratory samples will be 20 years, or as permitted by local regulations, to address further scientific questions related to mRNA-1273 or antirespiratory virus immune response. In addition, identifiable samples can be destroyed at any time at the request of the participant. During the study, or during the retention period, in addition to the analysis outlined in the study endpoints, exploratory analysis may be conducted using other Ab-based methodologies on any remaining blood or serum samples, including samples from participants who are screened but are not subsequently enrolled. These analyses will extend the search for other potentially relevant biomarkers to investigate the effect of mRNA-1273, as well as to determine how changes in biomarkers may relate to exposure and clinical outcomes. A decision to perform such exploratory research may arise from new scientific findings related to the drug class or disease, as well as reagent and assay availability.

10.2.11. Dissemination of Clinical Study Data

The Sponsor shares information about clinical trials and results on publically accessible websites, based on international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, EU clinical trial register (eu.ctr), as well as some national registries.

In addition, results from clinical trials are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance, and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available, the privacy of participants in clinical studies sponsored by the Sponsor is assured. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.2.12. Data Quality Assurance and Quality Control

Data collection is the responsibility of the clinical study staff at the study site under the supervision of the study site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

- All participant data relating to the study will be recorded in the eCRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the eCRF.
- The investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.
- The investigator must permit study-related monitoring, audits, IRB review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, CRO).

- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized study site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is less than 2 years. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Quality assurance includes all the planned and systematic actions that are established to ensure that the clinical study is performed and the data are generated, documented (recorded), and reported according to ICH GCP and local/regional regulatory standards.

A QA representative from the Sponsor or a qualified designee, who is independent of and separated from routine monitoring, may periodically arrange inspections/audits of the clinical study by reviewing the data obtained and procedural aspects. These inspections may include on-site inspections/audits and source data checks. Direct access to source documents is required for the purpose of these periodic inspections/audits.

10.2.13. Data Collection and Management

This study will be conducted in compliance with ICH CGP guidelines. This study will also be conducted in accordance with the most recent version of the Declaration of Helsinki.

This study will use electronic data collection to collect data directly from the study site using eCRFs. The investigator is responsible for ensuring that all sections of each eCRF are completed promptly and correctly and that entries can be verified against any source data.

Study monitors will perform source document verification to identify inconsistencies between the eCRFs and source documents. Discrepancies will be resolved in accordance with the principles of GCP. Detailed study monitoring procedures are provided in the Clinical Monitoring Plan.

Adverse events will be coded with MedDRA. Concomitant medications will be coded using WHO - Drug Dictionary.

10.2.14. Source Documents

Source documents are original documents or certified copies, and include, but are not limited to, eDiaries, medical and hospital records, screening logs, informed consent/assent forms, telephone contact logs, and worksheets. Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's study site.

Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

The Sponsor or its designee requires that the investigator prepare and maintain adequate and accurate records for each participant treated with the IP. Source documents such as any hospital, clinic, or office charts, and the signed ICFs are to be included in the investigator's files with the participant's study records.

10.2.15. Retention of Records

The principal investigator must maintain all documentation relating to the study for a period of at least 2 years after the last marketing application approval or, if not approved, 2 years following the discontinuance of the test article for investigation. If this requirement differs from any local regulations, the local regulations will take precedence unless the local retention policy is > 2 years.

If it becomes necessary for the Sponsor or the regulatory authority to review any documentation relating to the study, the investigator must permit access to such records. No records will be destroyed without the written consent of the Sponsor, if applicable. It is the responsibility of the Sponsor to inform the investigator when these documents no longer need to be retained.

10.2.16. Study and Site Closure

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the investigators, the IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participants and should assure appropriate participant therapy and/or follow-up.

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor.

The investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or investigator may include but are not limited to:

- Continuation of the study represents a significant medical risk to participants
- Failure of the investigator to comply with the protocol, the requirements of the IRB or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the investigator
- Discontinuation of further mRNA-1273 development

Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed.

10.2.17. Publication Policy

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.

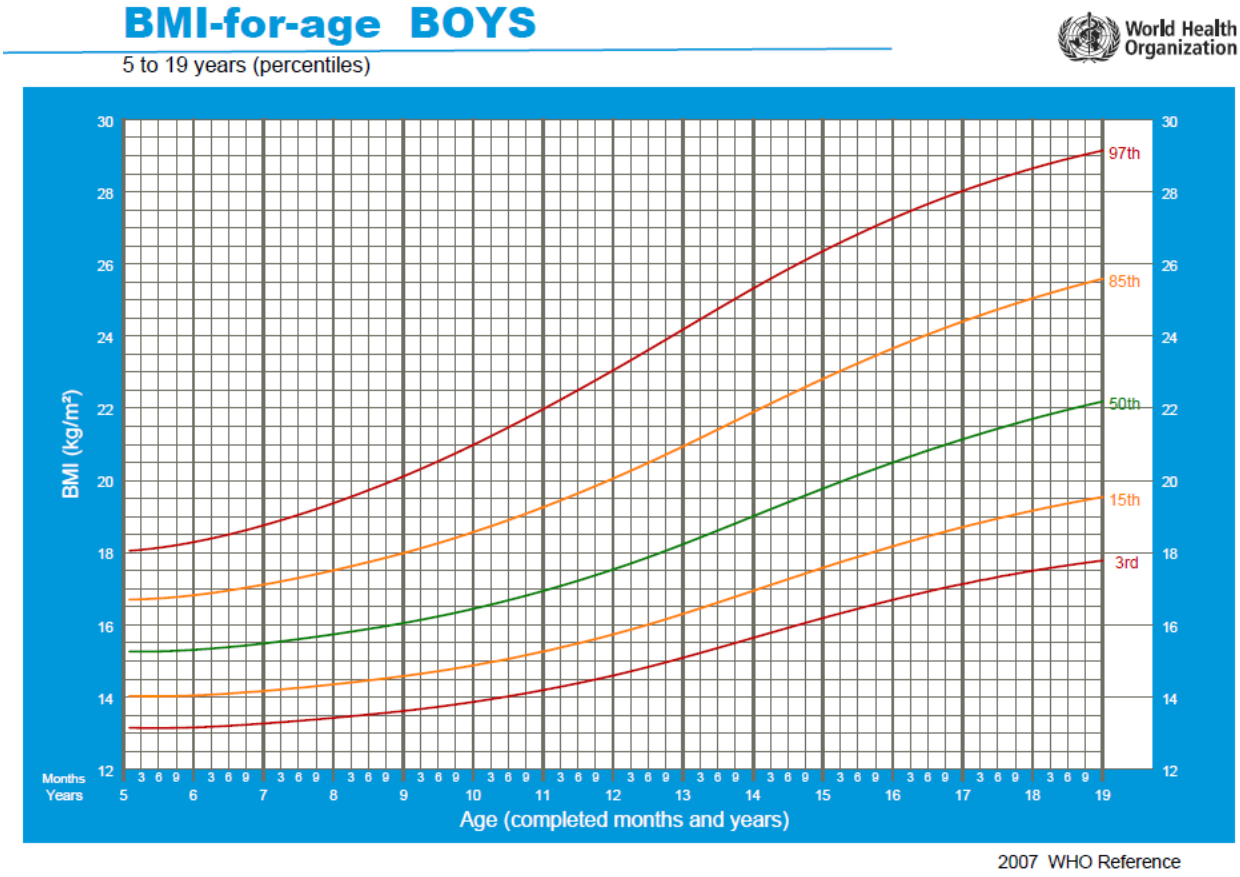
The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual study site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

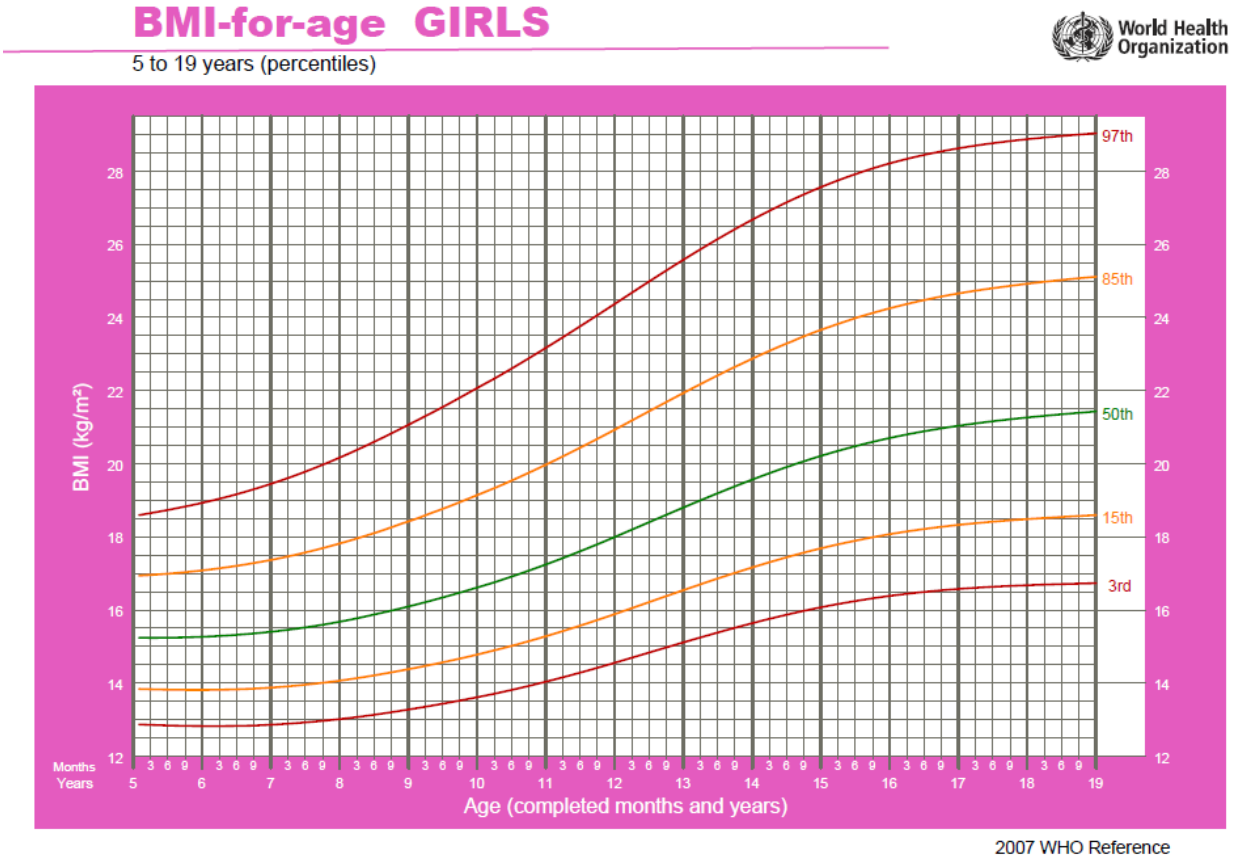
The clinical study plan and the results of the study will be published on www.ClinicalTrials.gov in accordance with 21 CFR 50.25(c). The results of and data from this study belong to the Sponsor.

10.2.18. Body Mass Index (BMI) Charts for Boys and Girls

For boys aged 5 through 19 years:



For girls aged 5 through 19 years:



10.3. APPENDIX 3: Contraceptive Guidance

Woman of Childbearing Potential (WOCBP)

Females of childbearing potential are those who are considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below). If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study treatment, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal
2. Premenopausal, surgically sterile female with 1 of the following:
    a. Documented complete hysterectomy
    b. Documented surgical sterilization

    For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, Mullerian agenesis, androgen insensitivity), investigator discretion should be applied in determining study entry.

    Note: Documentation can come from the study site personnel's review of the participant's medical records, medical examination, or medical history interview.

Contraception Guidance:

Adequate female contraception is defined as consistent and correct use of an FDA-approved contraceptive method in accordance with the product label. For example:

- Barrier method (such as condoms, diaphragm, or cervical cap) used in conjunction with spermicide
- Intrauterine device
- Prescription hormonal contraceptive taken or administered via oral (pill), transdermal (patch), subdermal, or IM route
- Sterilization of a female participant's monogamous male partner prior to entry into the study

Note that periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.

Signature Page for VV-CLIN-001208 v1.0

Approval	Jacqueline Miller Clinical 05-Nov-2020 16:12:31 GMT+0000

Approval	Roderick McPhee Medical 06-Nov-2020 13:02:24 GMT+0000

Approval	Charbel Haber Regulatory 09-Nov-2020 19:32:16 GMT+0000

Approval	Conor Knightly Clinical 10-Nov-2020 13:58:52 GMT+0000

Approval	Melissa Rossi Medical 11-Nov-2020 19:57:14 GMT+0000

Signature Page for VV-CLIN-001208 v1.0

ModernaTX, Inc.

Protocol mRNA-1273-P203

A Phase 2/3, Randomized, Observer-Blind, Placebo-Controlled Study to Evaluate the Safety, Reactogenicity, and Effectiveness of mRNA-1273 SARS-CoV-2 Vaccine in Healthy Adolescents 12 to < 18 Years of Age

Statistical Analysis Plan

SAP Version 2.0
Version Date of SAP: 7 May 2021

Prepared by:

PPD
3575 Quakerbridge Road
Suite 201
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List of Abbreviations

Abbreviation	Definition
AE	adverse event
AR	adverse reaction
BMI	body mass index
bAb	binding antibody
CI	confidence interval
CRO	contract research organization
CSP	clinical study protocol
CSR	clinical study report
DHHS	Department of Health and Human Services
eCRF	electronic case report form
eDiary	electronic diary
ELISA	enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
FAS	full analysis set
GM	geometric mean
GMFR	geometric mean fold rise
GMT	geometric mean titer
GMR	geometric mean ratio
IgG	immunoglobulin G
IP	investigational product
IRT	interactive response technology
LLOQ	lower limit of quantification
MAAEs	medically-attended adverse events
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
nAb	neutralizing antibody
OL	open-label
PP	per-protocol
PT	preferred term
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Statistical Analysis System
SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
ULOQ	upper limit of quantification
WHO	World Health Organization
WHODD	World Health Organization drug dictionary

1. Introduction

This statistical analysis plan (SAP), which describes the planned analyses for Study mRNA-1273-P203, is based on the most recent approved clinical study protocol (CSP), Version Amendment 1, dated 23-Mar-2021. The most recent approved electronic case report form (eCRF) Version 2.2, dated 15-DEC-2020.

In addition to the information presented in the statistical analysis plan section of the protocol (Section 8) which provides the principal features of analyses for this study, this SAP provides statistical analysis details/data derivations. It also documents modifications or additions to the analysis plan that are not "principal" in nature and result from information that was not available at the time of protocol finalization.

Study mRNA-1273-P203 is a Phase 2/3, randomized, observer-blind, placebo-controlled study to evaluate the safety, reactogenicity, and effectiveness of messenger ribonucleic acid (mRNA)-1273 SARS-CoV-2 vaccine in healthy adolescents who aged 12 to <18 years.

PPD Biostatistics and programming team, designee of Moderna Biostatistics and Programming department, will perform the statistical analysis of the safety, reactogenicity, and effectiveness data; Statistical Analysis System (SAS) Version 9.4 or higher will be used to generate all statistical outputs (tables, figures, listings, and datasets). The SAP will be finalized and approved prior to the primary analysis clinical database lock and treatment unblinding for the study. If the methods in this SAP differ from the methods described in the protocol, the SAP will prevail.

In this document, subject and participant are used interchangeably; injection of IP, injection, and dose are used interchangeably; vaccination group and treatment group are used interchangeably.

2. Study Objectives

2.1. Primary Objective

The primary objectives are the following:

- To evaluate the safety and reactogenicity of 100 µg of mRNA-1273 vaccine administered in 2 doses 28 days apart.

- To infer efficacy of mRNA-1273 (100 µg, 2 doses 28 days apart), serum Ab responses obtained 28 days after the second injection of mRNA-1273 (Day 57) will be either:
    - Evaluated against an accepted Ab threshold of protection against COVID-19 (if established in Study P301)
    - Compared in primary vaccine response as measured by geometric mean (GM) values of serum Ab and seroresponse rate in P203 with those obtained from adult recipients (18-25 years of age) of mRNA-1273 in the clinical endpoint efficacy trial (Study P301)

2.2. Secondary Objectives

The secondary objectives are the following:

- To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of SARS-CoV-2 S2P-specific bAb through 1 year after dose 2.
- To evaluate the persistence of the immune response of mRNA-1273 vaccine (100 µg) administered in 2 doses 28 days apart, as assessed by the level of nAb through 1 year after dose 2.
- To evaluate the effect of mRNA-1273 on the incidence of SARS-CoV-2 infection compared with the incidence among placebo recipients.
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo.
- To evaluate the incidence of COVID-19 after vaccination with mRNA-1273 or placebo. COVID-19 is defined as clinical symptoms consistent with SARS-CoV-2 infection AND positive RT-PCR for SARS-CoV-2.

2.3. Exploratory Objectives

The exploratory objectives are the following:

- To evaluate the genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.
- To describe the ratio or profile of specific bAb relative to nAb in serum.

- To characterize the clinical profile and immune responses of participants with COVID-19 or with SARS-CoV-2 infection.
- To evaluate the incidence of asymptomatic SARS-CoV-2 infection after vaccination with mRNA-1273 or placebo in participants with serologic evidence of infection at baseline.

3. Study Endpoints

3.1. Primary Endpoints

The primary safety objective will be evaluated by the following safety endpoints:

- Solicited local and systemic adverse reactions (ARs) through 7 days after each injection.
- Unsolicited adverse events (AEs) through 28 days after each injection.
- Medically-attended AEs (MAAEs) through the entire study period.
- Serious AEs (SAEs) through the entire study period.
- AE of special interest (AESI) of multisystem inflammatory syndrome in children (MIS-C) through the entire study period.
- Vital sign measurements.
- Physical examination findings.

The primary immunogenicity objective will be evaluated by either:

- The proportion of participants with a serum Ab level at Day 57 ≥ an Ab threshold of protection. If an accepted serum Ab threshold of vaccine protection against COVID-19 is available, this analysis will form the basis to infer efficacy.
- The primary vaccine response as measured by GM value of serum antibody level and seroresponse rate from Study P203 vaccine recipients at Day 57 compared with those obtained from young adult vaccine recipients (18-25 years of age) at Day 57 in the clinical endpoint efficacy trial (Study P301). If a threshold is not available, efficacy will be inferred based on establishing noninferiority of adolescent (12 to < 18 years; this clinical study) to adult GM values of serum antibody level and seroresponse rate obtained in Study P301 (GM value 12 to < 18 years / GM value 18-25 years).

Seroresponse due to vaccination at a subject level may be defined as a change from below the LLOQ to equal to or above LLOQ, or a z-fold rise if baseline is equal to or above LLOQ. The definition of seroresponse may depend on assay-specific performance characteristics, and the table below lists the assay-specific definition of seroresponse for each assay/test of interest.

Assay Name	**Category**	**Test Name/ Description**	**Definition of Seroresponse**
Pseudovirus (PsVNT)	nAb	PsVNT50 (ID 50)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 3.3-foldrise
		PsVNT80 (ID 80)	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 2.3-foldrise
Anti-Spike ELISA	bAb	Anti-Spike VAC65 Spike IgG Antibody	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 4.6-foldrise
MSD multiplex	bAb	Anti-Spike	baseline <LLOQ: >=LLOQ baseline >=LLOQ: 1.9-foldrise

Among the two Pseudovirus tests, PsVNT50 and PsVNT80, PsVNT50 is considered the most appropriate measure of subject response because it falls in the middle of the dynamic range of the dilution response curve while PsVNT80 is close to the plateau and thus subject to restriction.

The GM and seroresponse rate comparisons between adolescents in P203 and young adults (18-25 years of age) in P301 will be compared for the bAb and nAb measures listed in the table above, with pseudovirus nAb PsVNT50 (ID50) considered as the primary assay test for the immunobridging.

3.2. Secondary Endpoints

The secondary objective will be evaluated by the following endpoints:

- The GM values of SARS-CoV-2 S2P-specific bAb on Day 1, Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2).

- The GM values of SARS-CoV-2-specific nAb on Day 1, Day 57 (1 month after dose 2), Day 209 (6 months after dose 2), and Day 394 (1 year after dose 2).
- The incidence of SARS-CoV-2 infection counted starting 14 days after the second dose of IP. SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:
    - bAb levels against SARS-CoV-2 nucleocapsid protein negative at Day 1 that becomes positive starting at Day 57 or later. OR
    - Positive RT-PCR counted starting 14 days after the second dose of IP.
- The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) counted starting 14 days after the 2nd dose of IP in participants with negative SARS-CoV-2 at baseline.
- The incidence of the first occurrence of COVID-19 starting 14 days after the second dose of IP, where COVID-19 is defined as symptomatic disease based on the following criteria:
    - The participant must have experienced at least TWO of the following systemic symptoms: Fever ($\geq 38^{o}$ C/$\geq 100.4^{o}$ F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s), OR
    - The participant must have experienced at least ONE of the following respiratory signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia; AND
    - The participant must have at least 1 NP swab, nasal swab, or saliva sample (or respiratory sample, if hospitalized) positive for SARS-CoV-2 by RT-PCR.
- The incidence of the first occurrence of the secondary COVID-19 case starting 14 days after the first dose of IP, and the secondary COVID-19 case starting 14 days after the second dose of IP.

  The secondary case definition of COVID-19 is defined by the following criteria:
    - One of the following systemic or respiratory symptoms: fever (temperature $> 38^{o}$C/$\geq 100.4^{o}$F), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste

or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea, AND

- At least one positive RT-PCR test for SARS-CoV-2

3.3. Exploratory Endpoints

The exploratory endpoints are the following:

- The incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR test performed at least 14 days after first dose, and by bAb levels against SARS-CoV-2 nucleocapsid protein (by Roche Elecsys) at Day 57.
- Alignment of genetic sequence of viral isolates with that of the vaccine sequence.
- Relative amounts or profiles of S protein-specific bAb and specific nAb levels/titers in serum.
- Description of clinical severity and immune responses of participants who are identified as infected by SARS-CoV-2 (COVID-19).
- GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x and 4x rise of bAb relative to baseline

4. Study Design

4.1. Overall Study Design

This is a two-part, Phase 2/3 study: Part A and Part B. Participants in Part A, the Blinded Phase of the study, are blinded to their treatment assignment.

Part B, the Open-label Interventional Phase of this study, is designed to offer participants who received placebo in Part A of this study and who meet the Emergency Use Authorization (EUA) eligibility criteria an option to receive mRNA-1273 in an open-label fashion (Figure 2). Participants who received mRNA-1273 (100 µg) in Part A of this study will proceed to Part B after they are unblinded and will continue to follow the Part A Schedule of Assessments (SoA).

4.1.1. Part A, the Blinded Phase

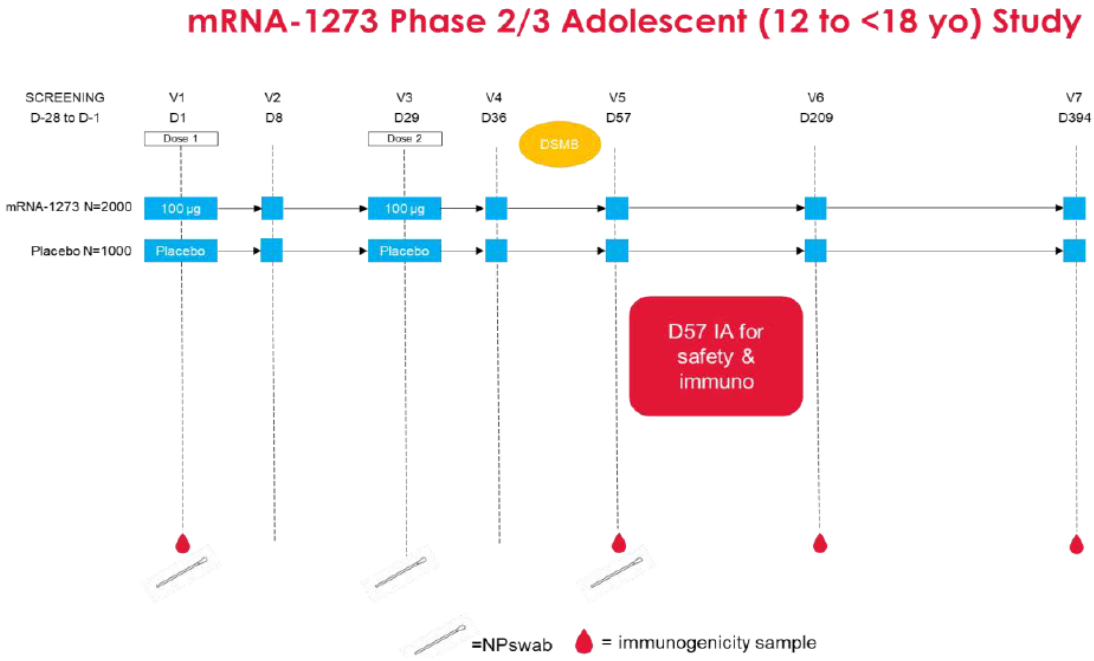
The blinded phase of this study is a randomized, observer-blind, randomized, and placebo-controlled study intended to infer the effectiveness of mRNA-1273 in an adolescent

population aged 12 to < 18 years. The study includes 2 arms: (i) 100 µg of mRNA-1273, and (ii) placebo. Approximately, 3,000 participants 12 to < 18 years of age will be randomly assigned in a 2:1 ratio to receive mRNA-1273 (n=2,000) or placebo (n=1,000).

The schematic of study arms and major study events for Part A is illustrated in Figure 1 and the Schedule of Assessments is provided in Appendix E.

The goal of the study is to seek an indication for use of mRNA-1273 (100 µg IM, given as 2 injections, 28 days apart) in the 12 to < 18 years age group. Each participant will receive one injection of mRNA-1273 or placebo on Day 1 and Day 29 and then be followed up for a total of 12 months following the second injection.

Figure 1 Study Design Schematic (Part A, Blinded Phase)



Abbreviation: D = day; DSMB = Data Safety Monitoring Board, IA = interim analysis, immuno = immunogenicity, NP = nasopharyngeal, V = visit, yo = years old.

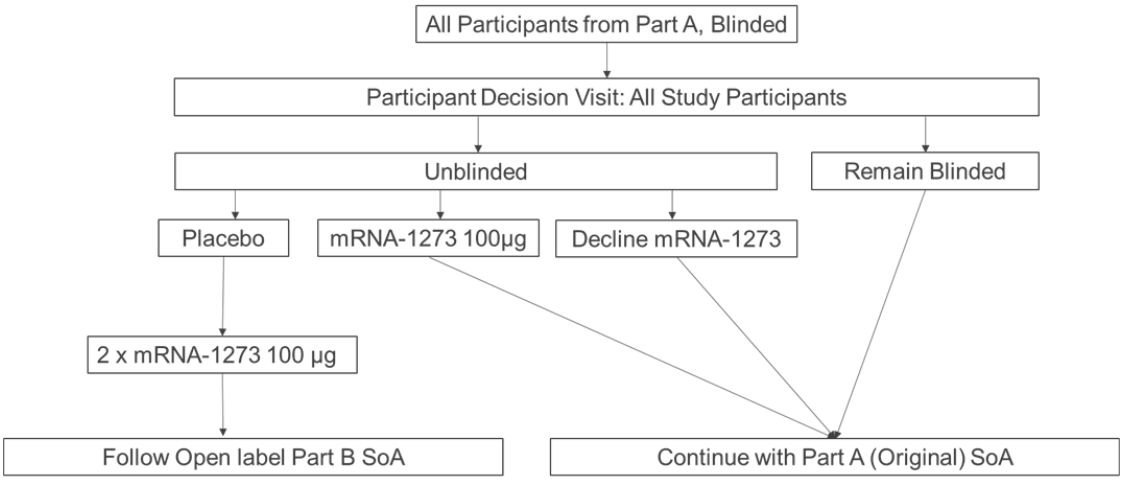
4.1.2. Part B, the Open-Label Observational Phase

Part B, the Open-Label Observational Phase of the study, will be prompted by the authorization of a COVID-19 vaccine under an Emergency Use Authorization (EUA) for any persons under the age of 18 years. Participants will be transitioned to Part B of the study as their age group becomes EUA-eligible. This transition permits all ongoing study participants to eventually be informed of the availability and eligibility criteria of any COVID-19 vaccine made available under an EUA and the option to offer all ongoing study

participants an opportunity to schedule a Participant Decision Visit to know their original treatment assignment (placebo vs. mRNA-1273 100 µg vaccine).

Part B provides the opportunity for study participants to be informed regarding the EUA, be unblinded to their original assignment (mRNA-1273 or placebo), and for those who previously received placebo, to actively request to receive 2 doses of mRNA-1273 (100 µg) vaccine.

Figure 2 Study Schema (Part B, Open-Label Observational Phase)



After the Participant Decision Clinic Visit (Protocol Table 8), all participants will follow the Part A SoA (Appendix E) or Part B SoA (Appendix F) as follows:

- Participants received placebo in Part A and consent to unblinding and to receiving 2 doses of mRNA-1273 in Part B: These participants will proceed to Part B and follow the SoA in Appendix F.
- Participants received 2 doses of mRNA-1273 in Part A and consent to unblinding: These participants will proceed to Part B of the study after they're unblinded, but will continue to follow the Part A SoA in Appendix E.
- Participants decline unblinding: These participants will remain in Part A and follow the SoA in Appendix E.

4.2. Statistical Hypothesis

- If an accepted serum Ab threshold of protection against COVID-19 is established for the primary immunogenicity objective, the null hypothesis is that the percentage of participants on mRNA-1273 with serum Ab equal to or above the established threshold

at Day 57 is ≤ 70% (ie, H_0: percentage of participants on mRNA-1273 ≤ 70% with serum Ab at Day 57 equal to or above the established threshold).

The study would be considered to meet the immunogenicity objective if the 95% confidence interval (CI) of percentage of participants on mRNA-1273 rules out 70% (lower bound of the 95% CI > 70%).

- If an accepted serum Ab threshold of protection against COVID-19 is not available for the primary immunogenicity objective, the immunogenicity analysis of primary vaccine response will be performed using the noninferiority tests of the two null hypotheses based on the two coprimary endpoints, respectively.
  - Coprimary endpoint 1: Ab geometric mean (GM) at Day 57

    The null hypothesis:

    H^1_0: immunogenicity response to mRNA-1273 as measured by Ab GM at Day 57 is inferior in adolescents (12 to < 18 years of age) receiving mRNA-1273 compared with that in young adults (18-25 years of age) receiving mRNA-1273 using Study P301 data.

    The noninferiority in Ab GM in adolescents compared with that in young adults (18-25 years of age) is demonstrated by meeting both success criteria:

    - The lower bound of the 95% CI of the geometric mean ratio (GMR) rules out 0.67 (lower bound > 0.67) using a noninferiority margin of 1.5.
    - The GMR point estimate > 0.8 (minimum threshold).

    The GMR is the ratio of the GM value of adolescents on mRNA-1273 in this study, Study P203, at Day 57 compared with the GM value of young adults (18-25 years of age) on mRNA-1273 in Study P301.

  - Coprimary endpoint 2: Ab seroresponse rate at Day 57

    The null hypothesis:

    H^2_0: immunogenicity response to mRNA-1273 as measured by seroresponse rate at Day 57 is inferior in adolescents (12 to < 18 years of age) receiving mRNA-1273 compared with that in adults (18-25 years of age)using mRNA-1273 Study P301 data

The noninferiority in seroresponse rate in adolescents compared with that in adults (18-25 years) is demonstrated by meeting both success criteria:

- The lower bound of the 95% CI of the seroresponse rate difference rules out -10% (i.e. lower bound > -10%) using the noninferiority margin of 10%.
- The seroresponse rate difference point estimate > -5% (minimum threshold)

The seroresponse rate difference is defined as the rate in adolescents receiving mRNA-1273 minus the rate in young adults (18-25 years of age) receiving mRNA-1273 from Study P301.

The study would be considered as meeting the primary immunogenicity objective if noninferiority is demonstrated based on both coprimary endpoints.

4.3. Sample Size and Power

The sample size of this study is driven by safety. Approximately 3,000 participants will be randomly assigned in a 2:1 ratio to receive mRNA-1273 and placebo. With 2,000 participants exposed to mRNA-1273, the study has at least 90% probability to observe at least 1 participant with an AE at a true 0.25% AE rate.

Serum samples from all participants will be collected and banked, a subset of participants will be selected, and their samples will be processed for immunogenicity testing (the Immunogenicity Subset).

Approximately 362 participants who receive mRNA-1273 will be selected for the Immunogenicity Subset, with a target of 289 participants in the PP Immunogenicity Subset (adjusting for approximately 20% of participants who may be excluded from the PP Immunogenicity Subset, as they may not have immunogenicity results due to any reason). The sample size of the Immunogenicity Subset may be updated with data from other mRNA-1273 studies or external data especially regarding a threshold of protection.

For the primary immunogenicity objective, with approximately 289 participants in the PP Immunogenicity Subset, the study will have > 90% power to rule out 70% with a 2-sided 95% CI for the percentage of mRNA-1273 participants exceeding the acceptable threshold if the true rate of participants exceeding the acceptable threshold is 80%.

If an acceptable Ab threshold of protection against COVID-19 is not available at the time of analysis, for the primary immunogenicity objective, noninferiority tests of two null hypotheses based on two coprimary endpoints, respectively, will be performed. The sample

size calculation for each of the two noninferiority tests was performed, and the larger sample size was chosen for the study.

- With approximately 289 participants in the PP Immunogenicity Subset in Study P203 and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) from Study P301, there will be 90% power to demonstrate noninferiority of the immune response as measured by Ab GM in adolescents in Study P203 at a 2-sided alpha of 0.05, compared with that in young adults (18-25 years of age) from Study P301 receiving mRNA-1273, assuming an underlying GMR value of 1, a noninferiority margin of 1.5, and a point estimate minimum threshold of 0.8. The standard deviation (SD) of the log-transformed levels is assumed to be 1.5.
- With approximately 289 participants in the PP Immunogenicity Subset in Study P203 and 289 participants in the PP Immunogenicity Subset in young adults (18-25 years of age) from Study P301, there will be at least 90% power to demonstrate noninferiority of the immune response as measured by seroresponse rate in adolescents in Study P203 at a 2 sided alpha of 0.05, compared with that in young adults (18-25 years of age) from Study P301 receiving mRNA 1273, assuming a true seroresponse rate of 85% in young adults (18-25 years of age) from Study P301, and a true seroresponse rate of 85% in adolescents in P203 (i.e., true rate difference is 0 compared to young adults from Study P301), a noninferiority margin of 10%, and a point estimate minimum threshold of -5% in seroresponse rate difference.

4.4. Randomization

Approximately 3,000 participants will be randomly assigned in a 2:1 ratio to receive mRNA-1273 and placebo for Part A. The randomization will be in a blinded manner using a centralized Interactive Response Technology (IRT) at the Day 1 visit, in accordance with pre-generated randomization schedules. There will be no strata for randomization in this study.

4.5. Blinding and Unblinding

Part A of this study is observer-blind. The investigator, study staff, study participants, site monitors, and Sponsor personnel (or its designees) will be blinded to the investigational product administered until study end or initiation of Part B, with certain exceptions, please

refer to Section 8.1 of the protocol for details. Planned analyses in this study include two interim analyses (refer to Section 6.8 for details) and a final analysis at the end of study. At the time of interim analysis, only pre-identified Sponsor and unblinded Contract Research Organization (CRO) team members as specified in the study Data Blinding Plan will be unblinded to review treatment level results and individual listings, please also refer to Section 6.8. Study sites will remain blinded to individual treatment assignments until the end of the study or initiation of Part B.

5. Analysis Populations

The following analysis sets are defined: Randomization Set, Full Analysis Set (FAS), Immunogenicity Subset, Per-protocol (PP) Immunogenicity Subset, Modified Intent-to-Treat (mITT) Set, Modified Intent-to-Treat-1 (mITT1) Set, Per-protocol (PP) Set for Efficacy, Solicited Safety Set, and Safety Set.

5.1. Randomization Set

The Randomization Set consists of all participants who are randomized in the study, regardless of the participant's treatment status in the study. Participants will be analyzed according to the treatment group to which they were randomized.

5.2. Full Analysis Set

The Full Analysis Set (FAS) consists of all randomized participants who received at least one dose of IP. Participants will be analyzed according to the treatment group to which they were randomized.

5.3. Immunogenicity Subset

A subset of participants in the FAS will be selected for immunogenicity testing. Immunogenicity Subset consists of

a) a subset of participants in the FAS, and

b) have baseline (Day 1) SARS-CoV-2 status available, and

c) have baseline and at least one post-injection antibody assessment for the analysis endpoint.

Participants will be analyzed according to the treatment group to which they were randomized.

5.4. Per-protocol (PP) Immunogenicity Subset

Per-Protocol (PP) Immunogenicity Subset consists of all participants in Immunogenicity Subset who meet all the following criteria:

a) Received planned doses of study vaccination per schedule

b) Complied with the timing of second dose of injection

c) Had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by *Roche Elecsys* Anti-SARS-CoV-2 assay) at baseline

d) Had baseline (Day 1) and Day 57 Ab assessment for the analysis endpoint

e) Had no major protocol deviations that impact key or critical data

The PP Immunogenicity Subset will serve as the primary population for the analysis of immunogenicity data in this study. Participants will be analyzed according to the treatment group to which they were randomized.

5.5. Modified Intent-to-Treat (mITT) Set

The Modified Intent-to-Treat (mITT) Set consists of all participants in the FAS who had no serologic or virologic evidence of prior SARS-CoV-2 infection (both negative RT-PCR test for SARS-CoV-2 and negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid) before the first dose of IP, i.e., all FAS participants excluding those with positive or missing RT-PCR test or serology test at baseline.

Participants will be analyzed according to the treatment group to which they were randomized.

5.6. Modified Intent-to-Treat-1 (mITT1) Set

The mITT1 Set consists of all participants in the mITT Set excluding those who received the wrong treatment (i.e., at least one dose received in Part A is not as randomized).

Participants will be analyzed according to the treatment group to which they were randomized.

5.7. Per-protocol (PP) Set for Efficacy

The Per-protocol (PP) Set for Efficacy consists of all participants in the FAS who meet all the following criteria:

a) Received planned doses of study vaccination

b) Complied with the timing of second dose of injection

c) Had a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by *Roche Elecsys* Anti-SARS-CoV-2 assay) at baseline

d) Had no major protocol deviations that impact key or critical efficacy data.

Participants will be analyzed according to the treatment group to which they were randomized.

5.8. Solicited Safety Set

The Solicited Safety Set consists of all participants who are randomized and received any study injection, and contribute any solicited AR data, i.e., have at least one post-baseline solicited safety assessment. The Solicited Safety Set will be used for the analyses of solicited ARs and participants will be included in the vaccination group corresponding to the study injection they actually received. In addition, the following Solicited Safety Set is defined for each injection separately.

The First (Second) Injection Solicited Safety Set consists of all subjects in the Solicited Safety Set who have received the first (second) study injection and have contributed any solicited AR data from the time of first (second) study injection through the following 6 days.

Participants will be analyzed according to the vaccination group a participant received, rather than the vaccination group to which the subject was randomized. A participant who was randomized to placebo but received any dose of mRNA-1273 at any injection will be included in the mRNA-1273 group in the Solicited Safety Set.

5.9. Safety Set

The Safety Set consists of all randomized participants who received any study injection. The Safety Set will be used for analysis of safety except for the solicited ARs. Participants will be included in the vaccination group corresponding to the vaccination they actually received. For a participant who was randomized to placebo but received any dose of mRNA-1273 at any injection, the participant will be included in the mRNA-1273 group in the Safety Set.

6. Statistical Analysis

6.1. General Considerations

The Schedule of Assessments is provided in Appendix E for Part A Blinded Phase, and Appendix F for Part B Open-Label Observational Phase.

Continuous variables will be summarized using the following descriptive summary statistics: the number of subjects (n), mean, standard deviation (SD), median, minimum (min), and maximum (max).

Categorical variables will be summarized using counts and percentages.

Baseline value, unless specified otherwise, is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before the first dose of IP. For immunogenicity tests, the baseline is defined as the most recent non-missing measurement (scheduled or unscheduled) collected before or on the date of first dose of IP.

For the summary statistics of all numerical variables unless otherwise specified, the display precision will follow programming standards. Please see Appendix A for variable display standards.

When count data are presented, the percentage will be suppressed when the count is zero in order to draw attention to the non-zero counts. A row denoted “Missing” will be included in count tabulations where specified on the shells to account for dropouts and missing values. The denominator for all percentages will be the number of subjects in that vaccination group within the analysis set of interest, unless otherwise specified.

Baseline SARS-CoV-2 status is determined by using virologic and serologic evidence of SARS-CoV-2 infection on or before Day 1.

Positive SARS-CoV-2 status at Baseline is defined as a positive RT-PCR test for SARS-CoV-2, and/or a positive serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by *Roche Elecsys* Anti-SARS-CoV-2 assay) on or before Day 1.

Negative status at Baseline is defined as a negative RT-PCR test for SARS-CoV-2 and a negative serology test based on bAb specific to SARS-CoV-2 nucleocapsid (as measured by *Roche Elecsys* Anti-SARS-CoV-2 assay) on or before Day 1.

Study day relative to the first injection will be calculated as below:

a) study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b) study day on or after the date of the first injection will be calculated as: date of assessment/event – date of the first injection + 1;

Study day relative to the most recent injection will be calculated as below:

a) study day prior to the first injection will be calculated as: date of assessment/event – date of the first injection;

b) study day on or after the date of the first injection but before the second injection (if applicable) will be calculated as: date of assessment/event – date of the first injection + 1;

c) study day on or after the date of the second injection will be calculated as: date of assessment/event – date of the second injection + 1; if study day is on the same day as the second injection, date and time will be compared with the second injection date and time.

For calculation regarding antibody levels/titers, antibody values reported as below LLOQ will be replaced by 0.5 × LLOQ. Values that are greater than the upper limit of quantification (ULOQ) will be converted to the ULOQ. Missing results will not be imputed.

The following **analysis periods or stages for safety analyses** will be used in this study:

- Up to 28 days after any vaccination: this stage starts at the day of each vaccination and continue through the earliest date of (the day of each vaccination and 27 subsequent days, next vaccination [if applicable]). This analysis period will be used as the primary analysis period for safety analyses including unsolicited AE, except for solicited AR, unless specified otherwise.

- Follow-up analysis period:

  For unsolicited AE or assessments that will be collected throughout the study, this analysis period starts from 28 days after the last injection date (i.e. the day of last injection + 28 days, regardless of number of injections received) and continues

until the earliest date of (study completion, discontinuation from the study, or death).

For assessments that will be collected at study visits (e.g. vital sign), if a subject receives two injections, this stage starts from the day after Day 57 visit and continues until the earliest date of (study completion, discontinuation from the study, or death); if a subject receives first injection only, this stage starts from the day after Day 29 visit and continues until the earliest date of (study completion, discontinuation from the study, or death).

- Overall period: this analysis period starts at the first injection on Day 1and continues through the earliest date of (study completion, discontinuation from the study, or death).

Unscheduled visits: Unscheduled visit measurements will be included in analysis as follows:

- In scheduled visit windows per specified visit windowing rules.
- In the derivation of baseline/last on-treatment measurements.
- In the derivation of maximum/minimum on-treatment values and maximum/minimum change from baseline values for safety analyses.
- In individual subject data listings as appropriate.

Visit windowing rules: The analysis visit windows for protocol-defined visits are provided in Appendix B.

Incomplete/missing data:

- Imputation rules for missing prior/concomitant medications, non-study vaccinations and procedures are provided in Appendix C.
- Imputation rules for missing AE dates are provided in Appendix D.
- For laboratory assessments, if majority of results are indefinite, imputation of these values will be considered. If the laboratory results are reported as below the LLOQ (e.g., <0.1), the numeric values will be imputed by 0.5 × LLOQ in the summary. If

the laboratory results are reported as greater than the ULOQ (e.g., >3000), the numeric values will be imputed by ULOQ in the summary.

- Other incomplete/missing data will not be imputed, unless specified otherwise.

Treatment groups:

The following vaccination groups will be used for summary purposes:

- Part A, Blinded Phase:
    - mRNA-1273
    - Placebo
- Part B or Long-term Analysis:
    - mRNA-1273: Participants from Part A mRNA-1273 group
    - Placebo: Participants from Part A placebo group who do not cross over to mRNA-1273
    - Placebo – mRNA-1273: Participants from Part A placebo group who cross over and receive mRNA-1273 in Part B

If a subject received any dose of mRNA-1273 at any injection, regardless of the treatment group the subject was randomized to, the subject will be included to mRNA-1273 100 μg group as the actual treatment group received for safety analyses.

Subgroup Analysis

Safety, efficacy and immunogenicity endpoints may be analyzed in select subgroups specified below as applicable:

- Baseline SARS-CoV-2 Status (Positive, Negative)
- Age (≥12 and <16 Years, ≥16 and <18 Years)
- Sex (Female, Male)
- Race
- Ethnicity

All analyses and data summaries/displays will be provided by vaccination group using appropriate analysis population unless otherwise specified.

All analyses will be conducted using SAS Version 9.4 or higher.

6.2. Background Characteristics

6.2.1. Subject Disposition

The number and percentage of subjects in the following categories will be summarized by vaccination group as defined in Section 6.1 based on Randomization Set:

- Randomization Set
- Full Analysis Set
- Immunogenicity Subset
- Per-protocol (PP) Immunogenicity Subset
- mITT Set
- mITT1 Set
- Per-protocol (PP) Set for Efficacy
- Solicited Safety Set
- Safety Set

The percentage will be based on subjects in that vaccination group within the Randomization Set (as randomized), except the Solicited Safety Set and Safety Set for which the percentages will be based on the vaccination group in the Safety Set (as treated).

The number of subjects in the following categories will be summarized based on subjects screened:

- Number of subjects screened
- Number and percentage of screen failure subjects and the reason for screen failure

The percentage of subjects who screen failed will be based on the number of subjects screened. The reason for screen failure will be based on the number of subjects who screen failed.

The number and percentage of subjects in each of the following disposition categories will be summarized by vaccination group based on the Randomization Set:

- Randomized by site
- Received each dose of IP
- Prematurely discontinued before receiving the second dose of IP and the reason for discontinuation
- Completed study
- Prematurely discontinued the study and the reason for discontinuation

A subject disposition listing will be provided, including informed consent, subjects who completed the study injection schedule, subjects who completed study, subjects who discontinued from study vaccine or who discontinued from participation in the study, with reasons for discontinuation. A separate listing will be provided for screen failure subjects with reasons for screen failure.

A subject who completed 12 months of follow up after the last injection received is considered to have completed the study.

6.2.2. Demographics

Descriptive statistics will be calculated for the following continuous demographic and baseline characteristics: age (years), weight (kg, z-score), height (cm, z-score), and body mass index (BMI) (kg/m^2, z-score). Number and percentage of subjects will be provided for categorical variables such as gender, race, ethnicity. The summaries will be presented by vaccination group as defined in Section 6.1 based on the FAS, Safety Set, Immunogenicity Subset, mITT Set, mITT1 Set, Per-protocol (PP) Immunogenicity Subset and Per-protocol (PP) Efficacy Set. If the Safety Set differs from the Randomization Set (e.g., subjects randomized but not received any study injection; subjects received study vaccination other than the vaccination group they were randomized to), the analysis will also be conducted using the Randomization Set. If the Immunogenicity Subset for SARS-CoV-2-specific bAb and the Immunogenicity Subset for SARS-CoV-2-specific nAb are the same, only one table will be provided. Otherwise, this will be generated for both the Immunogenicity Subset for SARS-CoV-2-specific bAb and Immunogenicity Subset for SARS-CoV-2-specific nAb. Same rule applies to the PP Immunogenicity Subset for

SARS-CoV-2-specific bAb and PP Immunogenicity Subset for SARS-CoV-2-specific nAb.

For screened failure subjects, age (years), as well as gender, race, ethnicity will be presented in a listing.

In addition, subjects with any inclusion and exclusion criteria violation will also be provided in a listing.

6.2.3. Medical History

Medical history data will be coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA).

The number and percentage of participants with any medical history will be summarized by SOC and PT based on the Safety Set. A participant will be counted only once for multiple events within each SOC and PT. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1273 and then alphabetically within SOC.

Medical history data will be presented in a listing.

6.2.4. Prior and Concomitant Medications

Prior and concomitant medications and non-study vaccination will be coded using the World Health Organization (WHO) drug dictionary (WHODD). The summary of concomitant medications will be based on the Safety Set. Categorization of prior, concomitant, and post medications is summarized in Appendix C Table 5.

The number and percentage of subjects using concomitant medications and non-study vaccination during the 7-day follow-up period (i.e., on the day of injection and the 6 subsequent days) and during the 28-day follow-up period after each injection (i.e., on the day of injection and the 27 subsequent days) will be summarized by vaccination groups as defined in Section 6.1 as follows:

- Any concomitant medications and non-study vaccination within 7 Days Post Injection
- Any concomitant medications and non-study vaccination within 28 Days Post Injection
- Seasonal influenza vaccine within 28 Days Post Injection

- Antipyretic or analgesic medication within 28 Days Post Injection

A summary table of concomitant medications and non-study vaccination that continued or newly received at or after the first injection through 28 days after the last injection will be provided by PT in descending frequency in the mRNA-1273 group.

Medications taken to prevent pain or fever will be collected on eDiary and summaries will be provided based on the Solicited Safety Set by vaccination group as defined in Section 6.1 for each injection (first or second) and any injection, including within 7 days after injection, beyond 7 days after injection and after injection.

Prior, concomitant and post medications and non-study vaccination will be presented in a listing.

Concomitant Procedures will be presented in a listing.

6.2.5. Study Exposure

Study IP administration data will be presented in a listing.

Study duration will be summarized since randomization, since the first injection, and since the second injection.

6.2.6. Major Protocol Deviations

Major protocol deviations are a subset of protocol deviations that may significantly impact the completeness, accuracy, or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being. Major protocol deviations rules will be developed and finalized before database lock.

The number and percentage of the subjects with each major protocol deviation type will be provided by vaccination group as defined in Section 6.1 based on the Randomization Set.

Major protocol deviations will be presented in a listing.

6.2.7. COVID-19 Impact

A listing will be provided for COVID-19 impact.

6.3. Safety Analysis

Safety and reactogenicity will be assessed by clinical review of all relevant parameters including solicited ARs (local and systemic), unsolicited AEs, SAEs, MAAEs, AESI, AEs leading to withdrawal from study vaccine and/or study participation, vital signs, and

physical examination findings. Unsolicited AEs will be coded by SOC and PT according to the MedDRA. The Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007) is used in this study for solicited ARs as presented in Table 3 from protocol.

All safety analyses will be based on the Safety Set, except summaries of solicited ARs which will be based on the Solicited Safety Set. All safety analyses will be provided by vaccination group unless otherwise specified.

6.3.1. Adverse Events

A treatment-emergent AE (TEAE) is defined as any event occurring during the study not before exposure to study vaccine or any event already present that worsens after exposure to study vaccine. [Note: worsening of a pre-existing condition after vaccination will be reported as a new AE.]

Adverse events will also be evaluated by the investigator for the coexistence of MAAE which is defined as an AE that leads to an unscheduled visit to a healthcare practitioner.

Unsolicited AEs will be coded by PT and SOC using MedDRA and summarized by vaccination group, and stage (up to 28 days after any vaccination, follow-up analysis period and overall stage; see Section 6.1 for definitions of vaccination group and stage).

All summary tables (except for the overall summary of AEs) for unsolicited AEs will be presented by SOC and PT for TEAEs with counts of subjects included. SOC will be displayed in internationally agreed order. PT will be displayed in descending order of frequency of mRNA-1273 and then alphabetically within SOC. When summarizing the number and percentage of subjects with an event, subjects with multiple occurrences of the same AE or a continuing AE will be counted once. Subjects will be presented according to the highest severity (the strongest relationship) in the summaries by severity (of related AEs), if subjects reported multiple events under the same SOC and/or PT.

Percentages will be based upon the number of subjects in the Safety Set within each vaccination group.

6.3.1.1. Incidence of Adverse Events

An overall summary of unsolicited TEAEs including the number and percentage of subjects who experience the following will be presented:

- Any unsolicited TEAEs

- Any serious TEAEs
- Any fatal TEAEs
- Any unsolicited medically-attended TEAEs
- Any unsolicited TEAEs leading to discontinuation from study vaccine
- Any unsolicited TEAEs leading to discontinuation from participation in the study
- Any unsolicited severe TEAEs
- Any AESI of MIS-C

The table will also include number and percentage of subjects with unsolicited TEAEs that are treatment-related in each of the above categories.

In addition, separate listings containing individual subject adverse event data for unsolicited AEs, unsolicited TEAEs leading to discontinuation from study vaccine, unsolicited TEAEs leading to discontinuation from participation in the study, serious AEs, unsolicited medically-attended AEs and AESI of MIS-C will be provided separately.

6.3.1.2. TEAEs by System Organ Class and Preferred Term

The following summary tables of TEAEs will be provided by SOC and PT using frequency counts and percentages (i.e., number and percentage of subjects with an event):

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related
- All serious TEAEs
- All serious TEAEs that are treatment-related
- All unsolicited TEAEs leading to discontinuation from study vaccine
- All unsolicited TEAEs leading to discontinuation from participation in the study
- All unsolicited Severe TEAEs
- All unsolicited Severe TEAEs that are treatment-related
- All unsolicited medically-attended TEAEs
- All unsolicited medically-attended TEAEs that are treatment-related

- All AESI of MIS-C

6.3.1.3.TEAEs by Preferred Term

A summary table of all unsolicited TEAEs will be provided. PTs will be sorted in a descending order according to the frequency in mRNA-1273 group.

6.3.1.4.TEAEs by System Organ Class, Preferred Term and Severity

The following summary tables of TEAEs will be provided by SOC, PT, and maximum severity (mild < moderate < severe) using frequency counts and percentages:

- All unsolicited TEAEs
- All unsolicited TEAEs that are treatment-related

6.3.2. Solicited Adverse Reactions

An AR is any AE for which there is a reasonable possibility that the test product caused the AE. The term “Solicited Adverse Reactions” refers to selected signs and symptoms occurring after injection administration during a specified post-injection follow-up period (day of injection and 6 subsequent days). The solicited ARs are recorded by the subject in eDiary. The occurrence and intensity of selected signs and symptoms is actively solicited from the participant during a specified post-injection follow-up period (day of injection and 6 subsequent days), using a pre-defined checklist (i.e., solicited ARs).

The following local ARs will be solicited by the eDiary: pain at injection site, erythema (redness) at injection site, swelling (hardness) at injection site, and localized axillary swelling or tenderness ipsilateral to the injection arm.

The following systemic ARs will be solicited by the eDiary: headache, fatigue, myalgia (muscle aches all over the body), arthralgia (aching in several joints), nausea/vomiting, rash, fever, and chills.

The solicited ARs will be graded based on the grading scales presented in Table 3 in the protocol, modified from the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials (DHHS 2007). Investigator will assess Grade 4 events (with exception of fever).

If a solicited local or systemic AR continues beyond 7 days post injection, the participant will be prompted to capture solicited local or systemic AR in the eDiary until resolution.

All solicited ARs (local and systemic) will be considered causally related to injection.

Analyses of solicited ARs will be provided by treatment group for each injection (first or second) based on the associated subset of Solicited Safety Set, i.e. First (Second) Injection Solicited Safety Set; and for any injection based on the Solicited Safety Set, unless otherwise specified.

The number and percentage of subjects who reported each individual solicited local AR (has a severity grade of Grade 1 or greater) and solicited systemic AR (has a severity grade of Grade 1 or greater) during the 7-day follow-up period after each injection will be tabulated by vaccination group, severity grade, and injection. The number and percentage of subjects who reported each individual solicited AR will also be summarized by vaccination group, severity grade, days of reporting and injection.

The number and percentage of subjects experiencing fever (a temperature greater than or equal to 38.0°C/100.4°F by the oral, axillary, or tympanic route) by severity grade will be provided.

A two-sided 95% exact confidence interval (CI) using the Clopper-Pearson method will be provided for the percentage of subjects who reported any solicited local AR, solicited systemic AR, or any solicited AR.

The onset of individual solicited AR is defined as the time point after each injection at which the respective solicited AR first occurred. The number and percentage of subjects with onset of individual solicited AR will be summarized by vaccination group, study day relative to the corresponding injection (Day 1 through Day 7), and injection.

The number of days reporting each solicited AR will be summarized descriptively and for the following time windows (1-2 days, 3-4 days, 5-6 days, and >=7 days) by vaccination group, and injection. The number of days will be calculated as the days of the solicited AR is reported within the 7 days of injection including the day of injection, no matter it is intermittent or continued. If the solicited AR continues beyond 7 days, the days a solicited AR is reported after 7 days will be included (e.g., an event that lasted 5 days in the first 7 days post injection and 3 days beyond 7 days post injection, the duration will be reported as 8 (5+3) days.)

6.3.3. Pregnancy Tests

A point-of-care urine pregnancy test will be performed at the Screening Visit (Day 0) and before each vaccine dose. At any time, a pregnancy test either via blood or point-of-care

urine can be performed, at the discretion of the investigator. A by-subject listing will be provided for pregnancy tests.

6.3.4. Vital Sign Measurements

Vital sign measurements, including systolic and diastolic blood pressures, heart rate, respiratory rate, and body temperature, will be presented in a data listing. The values meeting the toxicity grading criteria will be flagged in the data listing. The abnormalities meeting the toxicity grading criteria (Grade 2 or higher) in any vital sign measurement will be listed separately. If a subject has a vital sign result with Grade 2 or higher abnormality at any post injection visit, then all results of vital sign measurement for that subject will be presented in the listing.

Observed values and changes from baseline for all vital sign measurements will be summarized at each visit by vaccination group as defined in Section 6.1. Shift from baseline in the toxicity grades at each visit and shift from baseline in the toxicity grades to the worst post-baseline result will also be summarized by vaccination group.

6.4. Immunogenicity Analysis

The analyses of immunogenicity will be based on the PP Immunogenicity Subset and Immunogenicity Subset. The PP Immunogenicity Subset is the primary analysis population used in the immunogenicity analyses, unless otherwise specified. Subjects will be included in the treatment group to which they were randomized.

The GMT and geometric mean (GM) level will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(t_i)}{n}\right\}}$$

where $t_1, t_2, \ldots, t_n$ are n observed immunogenicity titers or levels.

The geometric mean fold-rise (GMFR) measures the changes in immunogenicity titers or levels within subjects. The GMFR will be calculated using the following formula:

$$10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}\left(v_{ij}/v_{ik}\right)}{n}\right\}} = 10^{\left\{\frac{\sum_{i=1}^{n}\log_{10}(v_{ij})-\log_{10}(v_{ik})}{n}\right\}}$$

where, for n subjects, v_{ij} and v_{ik} are observed immunogenicity titers or levels for subject i at time points j and k, $j \neq k$

6.4.1. Sampling of the Immunogenicity Subset

For the primary analysis of immunogenicity, and charactering immunogenicity of the vaccine, a simple sampling method will be used for measuring bAb and nAb data from a sampled subset of trial participants.

Sampling Plan

The first 550 participants enrolled in Part A who meet all the criteria below will be selected.

- The participant is in Full Analysis Set.
- Baseline SARS-CoV-2 status is not missing.

In such case, approximately 362 participants who receive mRNA-1273 will be selected for the Immunogenicity Subset, with a target of 289 participants in the PP Immunogenicity Subset (adjusting for approximately 20% of participants who may be excluded from the PP Immunogenicity Subset, as they may have baseline positive SAR-CoV-2 status, or have no immunogenicity results due to any reason).

For the noninferiority tests of Ab GM and seroresponse rate at Day 57 in adolescents in Study P203 compared with that in young adults (18-25 years of age) from Study P301 receiving mRNA-1273, an immunogenicity subset of 340 young adults from Study P301 will be randomly selected from all participants (18-25 years of age) receiving mRNA-1273, with a target of 289 participants in the PP Immunogenicity Subset (using same definition as in Study P203) after adjusting for approximately 15% of participants not meeting inclusion criteria for PP Immunogenicity Subset.

6.4.2. Immunogenicity Assessments

There will be two types of immunogenicity assessments:

- Serum bAb level against SARS-CoV-2 as measured by ELISA specific to the SARS-CoV-2 S protein
- Serum nAb titer against SARS-CoV-2 as measured by pseudovirus and/or live virus neutralization assays

6.4.3. Primary Analysis of Antibody-Mediated Immunogenicity Endpoints

If an accepted serum Ab threshold of protection against COVID-19 is available based on data from other mRNA-1273 studies or external data, the number and percentage of participants with Ab greater than or equal to the threshold at Day 57 will be provided with a 2-sided 95% CI using the Clopper-Pearson method. If the lower bound of the 95% CI on the mRNA-1273 group is > 70%, the primary immunogenicity objective of this study will be considered to be met.

The percentage of participants with serum Ab greater than or equal to the threshold with 95% CI will be provided at each postbaseline time point. The CI will be calculated using the Clopper-Pearson method.

If an accepted serum Ab threshold of protection against COVID-19 is not established, the noninferiority of primary vaccine response as measured by Ab GM and seroresponse rate in adolescents compared with those in young adults (18-25 years of age) receiving mRNA-1273 will be assessed. The study is considered to meet the primary immunogenicity objective if the noninferiority of the immune response to mRNA-1273 as measured by both GM and seroresponse rate at Day 57 is demonstrated in adolescents in this study at a 2-sided alpha of 0.05, compared with those in young adults (18-25 years of age) in Study P301 receiving mRNA-1273.

An ANCOVA model will be carried out with Ab at Day 57 as a dependent variable and a group variable (adolescents in P203 and young adults in P301) as the fixed variable. The GM values of the adolescents at Day 57 will be estimated by the geometric least square mean (GLSM) from the model. The GMR (ratio of GM values) will be estimated by the ratio of GLSM from the model. A corresponding 2-sided 95% CI will be provided to assess the difference in immune response for the adolescents in P203 compared to the young adults of 18-25 years of age in P301 at Day 57. The noninferiority of immune response to mRNA-1273 as measured by GM will be considered demonstrated if the lower bound of the 95% CI of the GMR is > 0.67 based on the noninferiority margin of 1.5, and GMR point estimate > 0.8 (minimum threshold).

The number and percentage (rate) of participants achieving Ab seroresponse at Day 57 will be summarized. The difference of seroresponse rates between adolescents receiving mRNA-1273 in P203 and young adults of 18-25 years of age receiving mRN-1273 in P301 will be calculated with 95% CI. The noninferiority in seroresponse rate of adolescents in P203 compared to adults of 18-25 years of age in P301 will be considered demonstrated if the

lower bound of the 95% of the seroresponse rate difference is > -10% based on the noninferiority margin of 10%, and the seroresponse rate difference point estimate > -5% (minimum threshold).

6.4.4. Secondary Analysis of Antibody-Mediated Immunogenicity Endpoints

For each group, the following evaluations will be performed at each time point at which blood samples are collected for immunogenicity (unless otherwise specified).

- GM level of SARS-CoV-2-specific bAb levels with corresponding 95% CI will be provided at each time point. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. GM level and corresponding 95% CI will be plotted at each timepoint. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.
- GM fold-rise of SARS-CoV-2-specific bAb levels with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1. The 95% CIs will be calculated based on the t-distribution of the log-transformed values then back transformed to the original scale for presentation. GM fold-rise and corresponding 95% CI will be plotted at each timepoint. The following descriptive statistics will be also provided at each time point: the number of subjects (n), median, minimum and maximum.

  Proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2 specific bAb levels from Visit Day 1 (baseline) at each post injection time points will be tabulated with 2-sided 95% Clopper Pearson CIs.
- GMT of SARS-CoV-2-specific nAb titers with corresponding 95% CI will be provided at each time point using the same method mentioned above.
- GMFR of SARS-CoV-2-specific nAb titers with corresponding 95% CI will be provided at each post-baseline timepoint over pre-injection baseline at Day 1 using the same method mentioned above.

  Proportion of subjects with fold-rise ≥ 2, fold-rise ≥ 3, and fold-rise ≥ 4 of serum SARS-CoV-2-specific nAb titers from Visit Day 1 (baseline) at each post-injection time points will be provided using the same method mentioned above.

- Proportion of subjects with seroresponse due to vaccination will be tabulated with 2-sided 95% Clopper-Pearson CIs at each post-baseline timepoint.
- Per the study protocol, if the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 (+7 days) as a result of the COVID-19 pandemic (self-quarantine or disruption of clinical site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the window may be extended to Day 29 + 21 days. More rigid visit window may be used in the Per-protocol Immunogenicity Subset as appropriate.

6.5. Efficacy Analysis

Efficacy analyses will be performed using the FAS, mITT, mITT1 and PP Set for Efficacy. The mITT1 Set is the primary analysis set for efficacy analysis of cases starting from 14 days after first dose, and PP Set for Efficacy is the primary analysis set used in the efficacy analyses for cases starting 14 days after second dose, unless otherwise specified. Subjects will be included in the treatment group which they were randomized.

Baseline SARS-CoV-2 status is described in Section 6.1. Baseline SARS-CoV-2 status, the serology test results based on *Roche Elecsys* assay at baseline, the RT-PCR test results at baseline will be summarized by treatment group.

Participants with baseline positive or missing SARS-CoV-2 status will be excluded from the PP Set for Efficacy.

In this study, the serology test results based on Roche Elecsys assay and the RT-PCR test results will be summarized by visit.

6.5.1. Endpoint Definition/Derivation

6.5.1.1.Derivation of SARS-CoV-2 Infection

This is a secondary efficacy endpoint, which is a combination of COVID-19 and asymptomatic SARS-CoV-2 infection for participants with negative SARS-CoV-2 status at baseline: the incidence of SARS-CoV-2 infection counted starting 14 days after the second dose of IP will be summarized by treatment group. SARS-CoV-2 infection will be defined in participants with negative SARS-CoV-2 at baseline:

- bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by *Roche Elecsys*) at Day 1 that becomes positive (as measured by *Roche Elecsys*) counted starting at Day 57 or later, OR

- Positive RT-PCR counted starting 14 days after the second dose of IP.

During the analysis, documented infection is counted starting 14 days after the second dose of IP, which requires positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid at Day 57 visit or later, or a positive RT-PCR result starting 14 days after the second dose of IP. Derivation of this secondary efficacy endpoint is summarized in Table 1 below.

Table 1. Derivation for SARS-CoV-2 Infection

	Post-baseline assessments		
Baseline SARS-CoV-2 Status	PCR test post baseline	bAb levels against SARS-CoV-2 Nucleocapsid	**Endpoint**: SARS-CoV-2 infection
Negative at Baseline	**Positive** (either at scheduled NP swab test, or at symptom-prompt NP swab test)		Case
Negative at Baseline		**Positive** (at scheduled Day 57 visit or later) as measured by *Roche Elecsys*	Case

The date of documented infection will be the earlier of:

- Date of positive post-baseline RT-PCR result, or
- Date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid

The time to the first SARS-CoV-2 infection will be calculated as:

Time to the 1st SARS-CoV-2 infection = Date of the 1st documented infection – Date of randomization + 1.

Cases will be counted starting 14 days after the second injection, i.e. date of documented infection ‑ Date of the 2nd injection ≥ 14.

SARS-CoV-2 infection cases will also be summarized based on tests performed at least 14 days after first dose of IP.

6.5.1.2.Derivation of Asymptomatic SARS-CoV-2 Infection

This is a secondary efficacy endpoint: the incidence of asymptomatic SARS-CoV-2 infection measured by RT-PCR and/or serology tests obtained at post-baseline visits counted starting 14 days after the second injection in participants with negative SARS-COV-2 status at baseline.

Asymptomatic SARS-CoV-2 infection is identified by absence of symptoms and infections as detected by RT-PCR or serology tests. Specifically:

- Absent of COVID-19 symptoms
- AND at least one from below:
    - bAb level against SARS-CoV-2 nucleocapsid protein negative (as measured by Roche Elecsys) at Day 1 that becomes positive (as measured by Roche Elecsys) counted starting at Day 57 or later, OR
    - Positive RT-PCR test at scheduled or unscheduled/illness visits

The date of documented asymptomatic infection is the earlier date of positive serology test result based on bAb specific to SARS-CoV-2 nucleocapsid due to infection, or positive RT-PCR at scheduled visits, with absence of symptoms.
The time to the asymptomatic SARS-CoV-2 infection will be calculated as:

Time to the asymptomatic SARS-CoV-2 infection = Date of asymptomatic SARS-CoV-2 infection test – Date of randomization + 1.

Asymptomatic SARS-CoV-2 infection cases will also be summarized based on tests performed at least 14 days after first dose of IP.

6.5.1.3.Derivation of COVID-19

This is a secondary efficacy endpoint: the incidence of the first occurrence of COVID-19 starting 14 days after the second dose of IP. COVID-19 is defined as symptomatic disease based on the criteria specified in Section 3.2. Cases are defined as participants meeting clinical criteria based on both symptoms for COVID-19 and positive RT-PCR test results.

Surveillance for COVID-19 symptoms will be conducted via biweekly telephone calls or eDiary. Subjects reporting COVID-19 symptoms, as defined in Section 7.3.2 of the protocol, will be arranged an illness visit to collect an NP swab.

For this efficacy endpoint, a COVID-19 case will be identified as a positive post-baseline RT-PCR test result, together with eligible symptoms, i.e. a positive PCR result of the eligible symptoms summarized below in Table 2.

Table 2. Derivation for COVID-19

	COVID-19
Post-baseline PCR result	Positive, **AND**
Systemic Symptoms	at least **TWO** of the following **systemic symptoms**: Fever (≥ 38ºC/≥ 100.4º F), chills, myalgia, headache, sore throat, new olfactory and taste disorder(s); **OR**
Respiratory symptoms	at least **ONE** of the following **respiratory** signs/symptoms: cough, shortness of breath or difficulty breathing, OR clinical or radiographical evidence of pneumonia.

The date of documented COVID-19 (case) will be the later date of ([2 systemic symptoms reported, or respiratory symptom reported] and, [date of positive PCR test]). Specifically, the date of documented COVID-19 will be the later date of the following two dates (date of positive PCR test, and the date of eligible symptom(s)), and the two dates should be within 14 days of each other.

- Date of positive PCR test,
- Date of eligible symptom(s), defined as earliest of
    - Respiratory symptom: earliest date of an eligible respiratory symptom is reported

- Systemic symptoms: earliest date of the 2nd eligible systemic symptom is reported

The time to the first occurrence of COVID-19 will be calculated as:

Time to the 1st occurrence of COVID-19 = Date of documented COVID-19 – Date of randomization + 1.

Cases will be counted starting 14 days after the second injection, i.e. date of documented COVID-19 - Date of the 2nd injection ≥ 14.

6.5.1.4.Derivation of Secondary Case Definition of COVID-19

This is a secondary efficacy endpoint: the incidence of the first occurrence of COVID-19 cases meeting the secondary case definition, starting 14 days after the first dose of IP, and COVID-19 cases starting 14 days after the second dose of IP.

The secondary case definition of COVID-19 is defined by the following criteria:

- One systemic or respiratory symptoms: fever (temperature > 38ºC/≥ 100.4ºF), or chills, cough, shortness of breath or difficulty breathing, fatigue, muscle aches, or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea, or vomiting or diarrhea, AND
- At least one positive RT-PCR test for SARS CoV-2

Date of the documented secondary definition of COVID-19 will be later date of:

- Date of the positive RT-PCR test (prompt by symptom)
- Date of eligible symptom for secondary definition of COVID-19, defined as the earliest date of first eligible symptom is reported

and the two dates should be within 14 days of each other.

Secondary case definition of COVID-19 cases will also be summarized based on tests performed after randomization, and based on tests performed at least 14 days after first dose of IP.

6.5.2. Analysis Method

The number and percentage of subjects who had an event will be summarized in the PP Set for Efficacy.

The incidence rate will be provided by vaccination group, calculated as the number of cases divided by the total person-time. The 95% CI of the incidence rate will be calculated using the exact method (Poisson distribution) and adjusted by person-time.

VE is defined as 1 – ratio of incidence rate (mRNA-1273 vs. placebo). The 95% CI of the ratio will be calculated using the exact method conditional upon the total number of cases adjusted by the total person-time.

Person-time is defined as the total time from randomization date to the date of event, last date of study participation, censoring time, or efficacy data cutoff date, whichever is earlier.

6.5.3. Sensitivity Analysis

Sensitivity analysis for these efficacy endpoints will be performed with the same methods described above based on the FAS, mITT Set, and mITT1 Set, and with cases counted starting at different time points.

6.6. Long-term Analysis

Long-term analysis will be performed including data collected in the Open-Label Observational Phase (Part B). Long-term analysis of applicable safety, efficacy, and immunogenicity endpoints will be summarized descriptively by treatment cohort without treatment group comparison.

In the long-term safety analysis, unsolicited AEs (SAE, MAAE, and AE leading to discontinuation) and deaths will be summarized.

In the long-term immunogenicity analysis, nAb and bAb values will be summarized at specified timepoints.

In the long-term efficacy analysis, the incidence rates of COVID-19 and of SARS-CoV-2 infection cases will be counted starting 14 days after the second dose of IP for participants in treatment cohorts of mRNA-1273 and Placebo, or starting 14 days after the second dose of mRNA-1273 for participants in the Placebo-mRNA-1273 Cohort. Incidence rate with

95% CI adjusting for person-time will be provided. The incidence rate of asymptomatic SARS-CoV-2 infection will also be provided.

Table 3. Treatment Cohorts for the Long-term Analysis

Treatment Cohort	Description
mRNA-1273	Participants randomized to mRNA-1273 in the Blinded Phase.
Placebo	Participants randomized to Placebo in the Blinded Phase who do not cross over to mRNA-1273 in the Open-Label Observational Phase.
Placebo-mRNA-1273	Participants randomized to Placebo in the Blinded phase who cross over to mRNA-1273 in the Open-Label Observational Phase.

6.7. Exploratory Analysis

6.7.1. Exploratory Analysis of Immunogenicity

The below exploratory analyses of immunogenicity may be performed:

- The genetic and/or phenotypic relationships of isolated SARS-CoV-2 strains to the vaccine sequence.
- Descriptive summaries of the ratio or profile of specific bAb relative to nAb in serum during the study. The analysis may not be included in the Clinical Study Report (CSR).
- Descriptive summaries of clinical profile and immunologic endpoints to characterize participants with SARS-CoV-2 infection during the study.
- Descriptive summaries of GM and GMFR of bAb levels against SARS-CoV-2 nucleocapsid protein (quantitative IgG) and % of participants with 2x, 3x and 4x rise of bAb relative to baseline)

6.7.2. SARS-CoV-2 Exposure and Symptoms

SARS-CoV-2 reported exposure history and symptoms assessment will be assessed during the study.

The number and percentage of subjects who had close contact with a person with SARS-CoV-2 infection, reasons for exposure, subjects with any symptoms of potential

COVID-19, and subjects with each symptoms will be presented by visit and vaccination group as defined in Section 6.1. Descriptive statistics will be provided for length of exposure in days by vaccination group.

In addition, the following listings will be provided for subjects infected by SARS-CoV-2:

- Serum bAb level against SARS-CoV-2
- Serum nAb titer against SARS-CoV-2
- Solicited ARs
- Unsolicited AEs

6.8. Interim Analysis

Study Day 57 is the primary time point for assessment of immunogenicity in this study. . More than one interim analysis of immunogenicity, safety and efficacy data will be performed.

- The first interim analysis will be performed after at least1500 participants (1000 participants receiving mRNA-1273) have completed Day 57 (one month after dose 2, Part A). The scope will be safety and efficacy.
- The second interim analysis will be performed after Day 57 immunogenicity data are available for immunogenicity subset. The scope will be immunogenicity, safety and efficacy. This interim analysis will be considered as the primary analysis of immunogenicity.

The final analysis of all applicable endpoints will be performed after all participants have completed all planned study procedures. Results of this analysis will be presented in an end of study CSR, including individual listings.

6.9. Data Safety Monitoring Board

Safety oversight will be under the direction of a DSMB composed of external independent consultants with relevant expertise. Members of the DSMB will be independent from the study conduct and free of conflict of interest. The DSMB will have separate meetings by teleconference to review unblinded safety data when half of the study population (1,500 randomized participants) have reached Day 8 (1 week after dose 1) and again approximately when 25% (750), 50% (1,500), and 75% (2,250) of enrolled participants have reached Day 36 (1 week after dose 2). Recruitment will continue, as applicable, during the DSMB review

period. The DSMB will operate under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. Details regarding the DSMB composition, responsibilities, procedures, and frequency of data review will be defined in its charter.

The DSMB will convene on an ad hoc basis if any of the pause rules, described in protocol Section 6.4, are met. The DSMB will review all available unblinded study data to adjudicate any potential study pauses and make recommendations on further study conduct, including requesting additional information, recommending stopping the study, recommending changes to study conduct and/or the protocol, or recommending additional operational considerations due to safety issues that arise during the study.

7. Changes from Planned Analyses in Protocol

In Section 4.2, for the noninferiority in Ab GM in adolescents in P203 compared with that in young adults (18-25 years of age in P301), an additional success criterion on point estimate has been added in this SAP: the GMR point estimate > 0.8 (minimum threshold). Similarly, for the noninferiority in seroresponse rate in adolescents compared with that in adults (18-25 years of age), an additional success criterion on point estimate has been added in this SAP: the seroresponse rate difference point estimate > -5% (minimum threshold).

8. References

Department of Health and Human Services (DHHS), Food and Drug Administration, Center for Biologics Evaluation and Research (US). Guidance for industry: Toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventative vaccine clinical trials. September 2007 [cited 2019 Apr 10] [10 screens].

Available from:
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm091977.pdf.List of Appendices

9. List of Appendices

9.1. Appendix A Standards for Safety and Immunogenicity Variable Display in TFLs

Continuous Variables: The precision for continuous variables will be based on the precision of the data itself. The mean and median will be presented to one decimal place more than the original results; the SD will be presented to two decimal places more than the original results; the minimum and maximum will be presented to the same precision as the original results.

Categorical Variables: Percentages will be presented to 1 decimal place.

9.2. Appendix B Analysis Visit Windows for Safety and Immunogenicity Analysis

Safety and Immunogenicity Analysis will be summarized using the following analysis visit window for post injection assessments:

Step 1: If the safety and immunogenicity assessments are collected at scheduled visit, i.e. nominal scheduled visit, the data collected at scheduled visit will be used.

Step 2: If the safety and immunogenicity assessments are not collected at the scheduled visit, assessments collected at unscheduled visit will be used using the analysis visit windows described in Table 4 below.

If a subject has multiple assessments within the same analysis visit, the following rule will be used:

- If multiple assessments occur within a given analysis visit, the assessment closest to the target study day will be used.
- If there are 2 or more assessments equal distance to the target study day, the last assessment will be used.

Table 4. Visit Window

Visit	Target Study Day	Visit Window in Study Day
Nasopharyngeal Swabs for SARS-CoV-2		
Day 1	1 (Date of First Injection)	1, Pre-first-dose

Day 29 (Month 1)	29 (Date of Second Injection)	[2, 43]
Day 57 (Month 2)	57	[44, 133]
Day 209	209	≥134
Illness Visit Day 1	X (Date of NP Swab test)	X
Illness Visit Day 3	X+2	[X+1, X+2]
Illness Visit Day 5	X+4	[X+3, X+4]
Illness Visit Day 7	X+6	[X+5, X+6]
Illness Visit Day 9	X+8	[X+7, X+10]
Illness Visit Day 14	X+13	[X+11, X+16]
Illness Visit Day 21	X+20	[X+17, X+23]
Illness Visit Day 28	X+27	[X+24, X+34]
Vital Signs		
Day 1	1 (Date of First Injection)	≤1, Pre-first-dose
Day 1	1 (Date of First Injection)	1, Post-first-dose
Day 29 (Month 1)	29 (Date of Second Injection)	[2, 43] Pre-second-dose
Day 29 (Month 1)	29 (Date of Second Injection)	[2, 43] Post-second-dose
Day 57 (Month 2)	57	[44, 133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302
Illness Visit Day 1	X (Date of COVID-19 Confirmation)	X
Illness Visit Day 28	X+27	[X+2, X+34]
Immunogenicity		
Day 1	1 (Date of First Injection)	1, Pre-first-dose
Day 57 (Month 2)	57	[44,133]
Day 209 (Month 7)	209	[134, 301]
Day 394 (Month 13)	394	≥302
Illness Visit Day 1	X (Date of NP Swab test)	X
Illness Visit Day 28	X+27	[X+2, X+34]

9.3. Appendix A Imputation Rules for Missing Prior/Concomitant Medications and Non-Study Vaccinations

Imputation rules for missing or partial medication start/stop dates are defined below:

1. Missing or partial medication start date:
   - If only Day is missing, use the first day of the month, unless:
     - The medication end date is after the date of first injection or is missing AND the start month and year of the medication coincide with the start month and year of the first injection. In this case, use the date of first injection
   - If Day and Month are both missing, use the first day of the year, unless:
     - The medication end date is after the date of first injection or is missing AND the start year of the medication coincide with the start year of the first injection. In this case, use the date of first injection
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be treated as though it began prior to the first injection for purposes of determining if status as prior or concomitant.
2. Missing or partial medication stop date:
   - If only Day is missing, use the earliest date of (last day of the month, study completion, discontinuation from the study, or death).
   - If Day and Month are both missing, use the earliest date of (last day of the year, study completion, discontinuation from the study, or death).
   - If Day, Month and Year are all missing, the date will not be imputed, but the medication will be flagged as a continuing medication.

In summary, the prior, concomitant or post categorization of a medication is described in Table 5 below.

Table 5. Prior, Concomitant, and Post Categorization of Medications and Non-study Vaccinations

	Medication Stop Date		
Medication Start Date	**< First Injection Date of IP**	**≥ First Injection Date and ≤ 28 Days After Last Injection**	**> 28 Days After Last Injection [2]**
< First injection date of IP [1]	P	P, C	P, C, A
≥ First injection date and ≤ 28 days after last injection	-	C	C, A
> 28 days after last injection	-	-	A

A: Post; C: Concomitant; P: Prior
[1] includes medications with completely missing start date
[2] includes medications with completely missing end date

9.4. Appendix B Imputation Rules for Missing AE dates

Imputation rules for missing or partial AE start dates and stop dates are defined below:

1. Missing or partial AE start date:

- If only Day is missing, use the first day of the month, unless:
  - The AE end date is after the date of first injection or is missing AND the start month and year of the AE coincide with the start month and year of the first injection. In this case, use the date and time of first injection, even if time is collected.
- If Day and Month are both missing, use the first day of the year, unless:
  - The AE end date is after the date of first injection or is missing AND the start year of the AE coincides with the start year of the first injection. In this case, use the date of first injection

- If Day, Month and Year are all missing, the date will not be imputed. However, if the AE end date is prior to the date of first injection, then the AE will be considered a pre-treatment AE. Otherwise, the AE will be considered treatment-emergent.

2. Missing or partial AE end dates will not be imputed.

9.5. Appendix E Schedule of Assessments (Part A, Blinded Phase)

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209/ Participant Decision Visit [3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	± 3	± 3	- 28/+ 56	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Informed consent/assent form, demographics, concomitant medications, medical history	X											
Revised informed consent/assent form									X			
Review of inclusion and exclusion criteria	X	X										
Physical examination including vital signs, height, weight[6]	X	X		X		X			X			X

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209/ Participant Decision Visit[3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	± 3	± 3	- 28/+ 56	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Pregnancy test[7]	X	X		X								
Randomization		X										
Study injection (including 60-minute postdose observation period)		X		X								
Blood sample for vaccine immunogenicity[8]		X				X			X			X
Nasopharyngeal swab sample for SARS-CoV-2[9]		X		X		X			X			
Surveillance for COVID-19/ Illness visit[10]/ Unscheduled visit		X	X	X	X	X	X	X	X	X	X	X
Convalescent Visit[11]		X	X	X	X	X	X	X	X	X	X	X
eDiary activation for recording solicited ARs (7 days)[12]		X		X								
Review of eDiary data			X		X							

Visit Number	0	1	2	3	4	5	-		6	-		7
Type of Visit	C	C	Virtual Call	C	Virtual Call	C	SFU		C	SFU		C
Month Time Point		M0		M1		M2	eDiary	SC	M7	eDiary	SC	M13
Study Visit Day	D0[1] (Screening)	D1 (Baseline)	D8[2]	D29[3]	D36[2, 3]	D57[2, 3]	Every 4 weeks D71 – D183[3, 4]	Every 4 weeks D85– D197[3, 5]	D209/ Participant Decision Visit[3]	Every 4 weeks D223– D363[3, 4]	Every 4 weeks D237– D377[3, 5]	D394[3]
Window Allowance (Days)	- 28		+ 3	+ 7	+ 3	+ 7	± 3	± 3	- 28/+ 56	± 3	± 3	± 14
Days Since Most Recent Injection	-	0	7	28/0	7	28	-	-	180	-	-	365
Follow-up safety telephone calls[13]								X		X		
Recording of unsolicited AEs		X	X	X	X	X						
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[14]		X	X	X	X	X	X		X	X		X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[14]		X	X	X	X	X	X		X	X		X
Recording of AESI (MIS-C)		X	X	X	X	X	X		X	X		X
Recording of concomitant medications and non-study vaccinations[14]		X	X	X	X	X						
Study completion												X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; AR = adverse reaction; C = clinic visit; COVID-19 = coronavirus disease 2019; D = day; eDiary = electronic diary; FDA = US Food and Drug Administration; ICF = informed consent form; IRB = institutional review board; M = month; MAAE = medically attended AE; MIS-C = multisystem inflammatory syndrome of children; SC = safety (telephone) call; SFU = safety follow-up; RT-PCR = reverse transcriptase polymerase chain reaction; SAE = serious adverse event; SARS-CoV-2 = Severe Acute Respiratory Syndrome coronavirus 2.

Note: In accordance with FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency (DHHS 2020), investigators may convert study site visits to home visits or telemedicine visits with the approval of the Sponsor.

1. Day 0 and Day 1 may be combined on the same day. Additionally, the Day 0 visit may be performed over multiple visits if preformed within the 28-day screening window.
2. All scheduled study visits should be completed within the respective visit windows. If the participant is not able to attend a study site visit as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), a safety telephone call to the participant should be made in place of the study site visit. The safety telephone call should encompass all scheduled visit assessments that can be completed remotely, such as assessment for AEs and concomitant medications (eg, as defined in scheduled safety telephone calls). Home visits will be permitted for all nondosing visits, with the exception of Screening, if a participant cannot visit the study site as a result of the COVID-19 pandemic. Home visits must be permitted by the study site IRB and the participant via informed consent/assent and have prior approval from the Sponsor (or its designee).
3. If the visit for the second dose (Day 29) is disrupted and cannot be completed at Day 29 +7 days as a result of the COVID-19 pandemic (self-quarantine or disruption of study site activities following business continuity plans and/or local government mandates for "stay at home" or "shelter in place"), the visit window may be extended to Day 29 + 21 days. When the extended visit window is used, the remaining study visits should be rescheduled to follow the inter-visit interval from the actual date of the second dose.
4. Safety follow-up via an eDiary questionnaire will be performed every 4 weeks from Day 71 to Day 183 and again from Day 223 to Day 363.
5. Safety follow-up via a safety telephone call will be performed every 4 weeks from Day 85 to Day 197 and again from Day 237 to Day 377.
6. Physical examination: A full physical examination, including height and weight, will be performed at Day 1, Day 29, Day 57, Day 209, and Day 394. BMI will be calculated only at Screening Visit (Day 0). Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. On each injection day before injection and again 7 days after injection, the arm receiving the injection should be examined and the associated lymph nodes should be evaluated. Any clinically significant finding identified during a study visit should be reported as an MAAE. Vital signs are to be measured pre- and post dose on days of injection (Day 1 and Day 29). When applicable, vital signs should be measured before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on Day 1 or Day 29 must have the visit rescheduled within the relevant visit window to receive the injection. Afebrile participants with minor illnesses can be enrolled at the discretion of the investigator.
7. Pregnancy test at Screening and Day 1 and before the second study injection will be a point-of-care urine test. At the discretion of the investigator, a pregnancy test either via blood or point-of-care urine test can be performed at any time.
8. Sample must be collected prior to dosing of injection on Day 1.
9. The nasopharyngeal swab sample will be used to ascertain the presence of SARS-CoV-2 via RT-PCR.
10. An unscheduled visit may be prompted by reactogenicity issues, illness visit criteria for Covid-19, or new or ongoing AEs. If a participant meets the prespecified criteria of suspicion for COVID-19, the participants will be asked to return within 72 hours or as soon as possible to the study site for an unscheduled illness visit, to include an NP swab sample (for RT-PCR testing) and other clinical evaluations. If a study site visit is not possible, a home visit may be arranged to collect the NP sample and conduct clinical evaluations. If a home visit is not possible, the participant will be asked to submit a saliva sample to the study site by a Sponsor-approved method. At this illness visit, the NP swab samples will be collected to evaluate for the presence of SARS-CoV-2 infection. NP swab samples will also be tested for the presence of other respiratory pathogens. In addition, the study site may collect an additional NP sample for SARS-CoV-2 testing to be able to render appropriate medical care for the study participant as determined by local standards of care. Additionally, clinical information will be carefully collected to evaluate the severity of the clinical case.
11. A convalescent visit will be scheduled approximately 28 days (+7 days) after diagnosis. At this visit, an NP swab sampling for viral PCR and a blood sample will

be collected for potential immunologic assessment of SARS-CoV-2 infection

12. Diary entries will be recorded by the participant at approximately 1 hour after injection while at the study site with instruction provided by study staff. Study participants will continue to record entries in the eDiary each day after they leave the study site, preferably in the evening, on the day of injection and for 6 days following injection. If a solicited local or systemic AR continues beyond Day 7 after vaccination, the participant will be prompted to capture details of the solicited local or systemic AR in the eDiary until the AR is resolves or the next IP injection occurs, whichever occurs first; capture of details of ARs in the eDiary should not exceed 28 days after each vaccination. Adverse reactions recorded in eDiaries beyond Day 7 should be reviewed either via telephone call or at the following study visit.
13. Trained study site personnel will call all participants to collect information relating to any AEs, MAAEs, SAEs, AEs leading to study withdrawal, information on concomitant medications associated with those events, and any nonstudy vaccinations. In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms.
14. All concomitant medications and nonstudy vaccinations will be recorded through 28 days after each injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (Day 394).

9.6. Appendix F Schedule of Assessments (Part B, Open-Label Phase for Subjects Who Previously Received Placebo)

Visit Number	7	8	9
Type of Visit	C	C	C
Study Visit Day	(D209/ Decision Visit) OL-D1	OL-D29	OL-D57[1]
Window Allowance (Days)	+7	-3/+7	±14
Days Since Most Recent Injection	0	28	28
Informed consent form	These assessments are already performed as part of the regular D209 visit		
Blood for vaccine immunogenicity			X
Nasopharyngeal swab sample for SARS-CoV-2[2]		X	X
Physical examination including vital signs[3]	PE including vitals performed as part of D209 visit.	X	X
	X Vitals post dose	X	
Pregnancy testing	X	X	
Study injection (including 30-minute post-dosing observation period)	X	X	
Recording of MAAEs and concomitant medications relevant to or for the treatment of the MAAE[5]	X	X	X
Recording of SAEs and concomitant medications relevant to or for the treatment of the SAE[4]	X	X	X
Recording of AESI (MIS-C)	X	X	X
Recording of concomitant medications and non-study vaccinations[5]	X	X	X

Abbreviations: AE = adverse event; AESI = adverse event of special interest; C = clinic visit; M = month; MAAE = medically attended AE; MIS-C = multisystem inflammatory syndrome of children; SC = safety (telephone) call; SFU = Safety Follow Up; SAE = serious adverse event.

1. After the OL-D57 visit, Part B participants will revert to the Part A SoA, re-entering at Day 265 as shown in Protocol Figure 4.
2. The nasopharyngeal swab sample, collected prior to vaccination on days of injection, will be used to ascertain the presence of SARS-CoV-2 via PCR.

3. Physical examination: A symptom-directed physical examination will be performed at OL-Day 1, OL-Day 29, and OL-D57. Symptom-directed physical examinations may be performed at other time points at the discretion of the investigator. Any clinically significant finding identified during a study visit should be reported as an MAAE. Vital signs are to be collected pre- and post-dosing on days of injection (OL-Day 1 and OL-Day 29). When applicable, vital sign measurements should be performed before blood collection. Participants who are febrile (body temperature ≥ 38.0°C/100.4°F) before injection on OL-Day 1 or OL-Day 29 must be rescheduled within the relevant window period to receive the injection. Afebrile participants with minor illnesses can be administered investigational product at the discretion of the investigator
4. Trained site personnel will call all participants to collect information relating to MAAEs, SAEs, AEs leading to study withdrawal, information on concomitant medications associated with those events, and any non-study vaccinations. In addition, study personnel will collect information on known participant exposure to someone with known COVID-19 or SARS-CoV-2 infection and on participant experience of COVID-19 symptoms. Sites will collect this information for diary days only if diary responses indicate the need for follow-up via telephone.
5. All concomitant medications and non-study vaccinations will be recorded through 28 days post-injection; all concomitant medications relevant to or for the treatment of an SAE or MAAE will be recorded from Day 1 through the final visit (OL-Day 209).